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SOME ASPECTS OF CORTICAL FUNCTION[1]

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IN his well-known book on Functional Localisation in the Frontal Lobes and Cerebellum, Fulton (1949, p. 13) contrasts the value of philosophical reflection and of recourse to experiment, as if they were alternative rather than complementary methods of study.

For those who have the training and skill and that lack of Franciscan sensibility necessary to the animal experimenter, it is doubtless wise to scorn the delights of philosophy and to live laborious days. It is, however, to be hoped that the results of their experiments will be submitted to a close and critical study, whether by the experimenter himself, as we could wish, or by the interested observer from the field of human neurology. For it cannot be denied that with the access of new knowledge and the destruction of old error has come much perplexity from conclusions that appear incompatible, or even contradictory.

In particular, one has found puzzling the results of investigation in man and animals of cortical function and I wish to think about three aspects of modern studies. These are the functions of the frontal areas (Fulton), the surprising results of removal of a diseased hemisphere in infantile hemiplegia and the unorthodox views of some much respected neurophysiologists and neurological surgeons on the seat of the highest level of the nervous system.

(1) FUNCTIONS OF THE FRONTAL AREAS (FULTON)

Studies of cortical function are based on the effects resulting from electrical stimulation in animals and in man, on activation of small areas of the cortex by application of strychnine—the effects in remote structures

[1]Presidential Address, Neurological Section, Royal Society of Medicine, October 4, 1951.

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being recorded electrically, on excision of areas of cortex or division of subcortical tracts and on the symptoms and signs resulting from disease.

Many of the conclusions drawn from such studies are conflicting and even contradictory and it is my aim to try to explain a few of the contradictions. For I believe that the confusion is sometimes due to unjustifiable simplification, to defective analysis of symptoms, to facile generalizations and to deductions beyond those warranted by the facts.

The brain has been too much regarded as a passive structure to which things can be done and too little as a highly reactive and adaptable organ which will do much to counter the injuries inflicted by disease or by the surgeon.

Again, in the investigation of the effects of electrical stimulation the artificiality of the procedure has been too much ignored. Even now when modification of the parameters of stimulation is recognized as important the stimuli are, I think, intensely unphysiological and appear to me comparable to testing skin sensibility with a red hot crowbar.

Neuronography by strychnine activation is a more physiological procedure and has already produced results of such extreme interest as the identifying of suppressor areas in the cortex but, significantly perhaps, most of the striking distant effects of electrical stimulation do not appear to result from this procedure.

In clinical study we have been at fault in the defective analysis we make of symptoms of disease, especially those involving higher functions, with a consequent multiplication of syndromes of poorly analysed content, and in the failure to seek, by extended and improved tests, for the illuminating fundamental deficiencies—a field of work in which the clinician can receive valuable aid from the psychologist. The very conception of cortical "centres" of function, especially of efferent function, though a useful mnemonic in practice, has been rightly challenged by Critchley (1951) as an inaccurate over-simplification.

Goldstein (1939) says that we learn more and more reliably the further our analysis of effects is carried and in the strict sense the examination of symptoms is never complete. There can be no doubt that many deductions drawn from symptoms would not be made if a full enough analysis of the symptoms were practicable.

The many fascinating studies on the body image indicate clearly the present need for drawing up and defining as accurately as possible a system of test procedures designed to give the best analysis of symptoms, a system which will need constant modification with increasing experience.

Electrical stimulation.—When a small area of the cortex receives a liminal electrical stimulus effects may result which have some relation to

the part which that area plays in the composite activity of the cortex. Such effects may reveal a neural connexion between the stimulated area and some distant part of the brain or spinal cord or sense organs.

In conscious man stimulation of the areas of sensory reception produces evidence of their sensory function in the form of crude sensations in consciousness, always accepted by the individual as artificial and not a part of his continuous field of consciousness. In the post-central gyrus crude, often indescribable, sensations in the appropriate area of the opposite side of the body result, in the striate area flashes, darkness, shadows, etc., and in the auditory area booming, ringing, noise or deafness. As Penfield and Rasmussen (1950) state the effects are either positive or negative, evoking or suppressing sensation. All we may deduce from this is that the stimulated points have some relation to body feeling, vision and hearing respectively. By varying the point of stimulation in the post-central and striate areas we may deduce that there is some spatial correspondence between the cortical area stimulated and its afferent connexions. But it is clear that if the manifold aspects of normal sensibility are mediated by these cortical areas electrical stimulation gives us no indication of the fact.

There are few areas of the cortex which are so well defined in their natural function as the visual cortex is. If electrical stimulation there provides such meagre evidence of this natural function we must not ignore its limitations or expect it to reveal the full aspects of natural function in areas of which we have less secure knowledge.

Penfield and Rasmussen also record that when they stimulated the appropriate Rolandic area in a patient who was talking at the time they stopped his speech (l.c., p. 96). He reported he was unable to speak. This provides further evidence that such excitation actually arrests physiological activity in the stimulated area, and there is much other evidence of this fact. So that whatever results from such excitation we may be reasonably certain that, positive or negative, it is not what goes on there in the intact normal processes of the brain.

This consideration is of the highest significance when as a result of applying an electrical stimulus say to the temporal lobe, as Penfield and Rasmussen state (l.c., p. 165), a dream appears in consciousness. Is it safe to say, as they do (l.c., p. 224), that this indicates that the neural process underlying memory is located there? May it not be that the stimulus has suppressed the normal activity of that cortex and that the dream is the resultant of the activity of the rest of the brain? It seems to me far more likely that with such complex activities an electrical stimulus would obliterate normal cortical activity rather than excite it, even more likely than that it does so in the primary sensory areas.

Turning to electrical stimulation of the pre-central motor cortex Chang

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and others (1947) using unipolar stimulation and threshold stimuli found that certain points in the pre-central cortex yielded only isolated contraction of a single muscle. From this we may deduce only that the cells stimulated could transmit their excitation directly or indirectly to the anterior horn cells of the contracting muscle. Stronger stimulation of neighbouring cells also produced contraction in the same and other muscles. These results indicate a closer association of one muscle with one area of the cortex than with other areas. There is ample evidence (Denny Brown and Botterell, 1948) that excision of the small area of cortex which they stimulated would not result in paralysis of the muscle which contracted. The conception of a motor centre for that muscle can hardly be justified. Nor, as they state, can the theory that the motor cortex is organized in a mosaic of strictly isolated individual muscle centres which spatially and temporally are activated like so many organ pipes to produce the harmony of normal movement.

The carefully reasoned arguments of Walshe (1947) on this matter are cogent. Willed movement, as he says, is fully co-ordinated movement and so contraction of single muscles never results from cortical motor action in normal man.

Fulton (l.c., p. 15) reports that Kaada, using square pulse waves of 10 milliseconds duration, has produced twitches in single muscles and has even produced a winking movement of the anal sphincter. Walshe would, I believe, say that such isolated activity was highly artificial and could not, even with practice, be reproduced voluntarily. The "wink" may not be especially significant but the difference is fundamental.

In the areas rostral to the pre-central gyrus, and in the orbital and cingulate gyri the effects of electrical stimulation are often autonomic (Fulton, l.c., p. 56 *et seq.*). In area 6, however, contralateral motor effects are produced, and in area 8 (Fulton, l.c., p. 58) conjugate deviation of the eyes to the opposite side. Penfield locates the area for contraversive eye and head turning widely in the pre-central area and area 6 in man (Penfield and Rasmussen, l.c., p. 74).

In animals the autonomic effects include change of pulse-rate and blood pressure, of gastric motility and secretion of respiratory rate and depth, and of pupil size; also eyelid movement, protrusion of the eyeball, lachrymation, erection of the hair, sweating, and salivation.

Penfield and Rasmussen (l.c., p. 77), on the other hand, describe very few of such effects from cortical stimulation in man, and from their extensive but still limited observations state "that there is little or no representation in the human cerebral cortex of the following autonomic systems: cardiovascular, pilomotor, sudomotor, urinary, temperature regulation, and tear secretion."

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They do recognize alimentary effects, apparently autonomic in derivation—certain sensations, and nausea and vomiting; these were not elicited from the frontal areas but from the Island of Reil. Their conclusions (l.c., p. 85) are that "it would appear that the important representation of the cardiovascular, sudomotor and pilomotor systems, and probably the respiratory system, are not to be found in the cerebral cortex but in grey matter located near the third ventricle." This difference between the conclusions regarding electrical stimulation of the frontal areas in lower animals and man—varied autonomic effects in the former, few and alimentary only in the latter—is, at first sight, baffling. But it may be largely explained by the following considerations. First Penfield and Rasmussen record few stimulations of the areas under discussion; next, they do not indicate that they systematically tested for autonomic responses (which would indeed be difficult in man) but they appear to have depended frequently on the patient's comments with regard to his sensations; and lastly it has been shown that many factors influence the effects elicited in animals. The type of electrical wave used, its duration and frequency and the total duration of stimulation all do so and Fulton (l.c., p. 60) refers to the opinion of L. Davey that the depth of anæsthesia and the anæsthetic used are important factors in determining the effects produced.

One presumes that liminal or only slightly supraliminal voltage is used in all cases, as is specifically stated by Penfield and Rasmussen who used saw-tooth waves of a fraction of a millisecond duration and a frequency of about 60 cycles per second at a voltage of from half to five volts. This parameter of stimulation is *quite different* from those recorded by the animal experimenters and Fulton states that cortical *autonomic* neurones are not activated by brief pulses or high frequencies such as Penfield and Rasmussen used. Livingston *et al.* (1948) have reported in the respiratory effects produced by stimulating the orbital gyrus in man a similar variation according to change in rate of stimulation.

So important is the frequency and duration of the stimulating wave that by varying these and stimulating the same points in area 8 of the macaque Livingston (quoted by Fulton, l.c., p. 58) has produced either lachrymation, or pupillary dilatation, or conjugate deviation of the eyes to the same side or to the opposite side. From a proximate and overlapping area movements of opening the eyelids, protrusion of the eyeballs and pupillary dilatation or the reverse movements can be elicited by other rates and duration of stimulation, and, more remarkably still, Davey (quoted by Fulton, l.c., p. 61) has produced *from the same area* vigorous peristalsis of the stomach and intestine and increase in the volume and concentration of the gastric juice.

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There is, in fact, so much evidence of the production of such autonomic effects from cortical stimulation of the frontal areas under consideration that Penfield and Rasmussen's conclusions to the contrary cannot be unreservedly accepted; even though the brains they examined were unanæsthetized and human.

Ablation of frontal cortex.—When, however, we come to consider the results of ablation or destruction of frontal cortex, expecting, perhaps naïvely, that removal of an area of known response on stimulation might give rise to effects of a comparable similar but negative character, one is again baffled by the lack of any such thing.

Penfield and Rasmussen (l.c., p. 93) state that "removal of very large areas, indeed of practically the whole frontal lobe on one side anterior to the precentral gyrus, results in an amazing lack of obvious defect," and one such case "demonstrated no alteration in behaviour except an impairment of those mental processes which are pre-requisite to planned initiative." Even at the time of removal of large regions near the frontal poles no loss of consciousness occurs and the patient will continue a conversation as Penfield says (l.c., p. 226) "unaware of the fact that he is being deprived of that area which most distinguishes his brain from that of a chimpanzee." After bilateral frontal gyrectomy Penfield (1948) concluded that if this transgressed bilaterally the borders of his superior intermediate frontal zone (Brodmann, area 8, posterior part of area 9 and anterior part of area 6) there resulted temporary mental confusion, incontinence, repetitive automatic movements and apathy or stupor while more anterior removals produced none of these symptoms. His psychologist found in addition a consistent slight drop in general intelligence, impairment of interest, and other psychological defects.

But one searches in vain for any reference to defects in autonomic activity. The same negative picture of autonomic effects from frontal area lesions is reported by Netsky and Starr (1948) though they found disturbances of sweating and vasomotor function in lesions of the pre-central and post-central cortex.

Perhaps the best illustration of the disparity between the results of stimulation and those of extirpation is afforded by the anterior cingulate gyrus. Here electrical stimulation effects are of three kinds, autonomic, motor and suppressor. In the first group there are dilatation of the pupil, pilo-erection, respiratory slowing and arrest, slowing of the heart, cardiac arrest, and blood pressure changes. In the second group there are slow tonic bilateral movements of the whole body, or vocalization and facial movements. As a suppressor area the effect of stimulation is

widespread suppression of cortical electrical activity and general relaxation of muscular contractions with loss of all deep reflexes.

If you spent all the necesary time thinking up what might conceivably result from removing an area that had such functions as those referred to, it is doubtful if you would ever guess how the brain behaves when deprived of this part. For the striking change is an alteration in the monkey's personality, summarized by Ward (1948) as acting as if it had lost its "social conscience," a characteristic, as we know, of the normal monkey, easily recognizable though, perhaps, not easy to measure. It will sit down on any available part of a companion monkey or take food from it without apparently expecting retaliation, and it neglects its personal appearance. But there is no story of hair that lies down, pupils that contract, or pulse and respiration abnormally fast.

It is clear that you could describe such behaviour in many ways. Smith (1944) noted it, and called it "tameness." What is really the fundamental loss is a subject for analysis probably beyond the powers of the animal psychologist. What seems clear is that one could not have predicted any such result from the effects of stimulation yet Ward describes these effects as the "functions" of this cortical area.

Now removal of the *sensory* areas of the cortex causes defects which might have been predicted in some degree from the known results of electrical stimulation and the same is, of course, true of the motor area. Crude and, in a sense, unnatural as are the effects of electrical stimulation in these areas they are, at least, of the same order of phenomena as are those of extirpation. But what part can we suppose the anterior cingulate gyrus plays in the behaviour of the normal monkey?

In the parietal lobe posterior to the post-central gyrus the only effect from electrical stimulation recorded by Penfield and Rasmussen (l.c., p. 220) was "in the area of parietal speech arrest in the dominant hemisphere." Here the effect was to cause the patient to name objects wrongly—aphasia. Yet we know from many observations that destructive lesions of the parietal lobe cause profound disorganization of the physiological and psychological fields in which integration of somatic, visual and auditory functions is concerned.

In the anterior temporal lobe, again, Penfield stimulating the cortex of patients subject to epileptic attacks arising from this region (and the qualification is important) caused to appear various illusions and hallucinations which, to him, appeared to associate this area especially with auditory and visual memory of things "on which the subject had focused his mind" in the past, either real events, or dreams.

In spite of this richness of function suggested by electrical stimulation removal of the major part of the temporal lobe does not seem to cause

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any defect in memory. They believe, however, that apparently identical patterns of activity exist in the opposite temporal lobe and they have not removed both temporal lobes. They quote Klüver and Bucy (l.c., p. 223) who recorded evidence suggesting loss of memory in the monkey from which both temporal cortices had been removed.

There seems, then, good reason for caution in deductions concerning natural function of the frontal cortex on the basis of the results of electrical stimulation. Such stimulation may cause a spread of activity to lower cells and eventuate in autonomic effects, but the same effects arise from stimulation elsewhere. So one would not expect removal of the cortical point in question to have any observable autonomic effect, and that seems to be the case. Even after bilateral frontal lobotomy post-operative autonomic disorders were persistent in only five of two hundred patients (Moore and others, 1948). Are, then, such effects to be regarded as coincidental, or wholly artificial?

I think not and will venture an hypothesis which synthesizes the facts without distorting them or straining credibility.

Walshe has emphasized that even the most isolated willed movement such as the flexion of a single terminal phalanx of a finger is never the result of a contraction of one muscle but of an integrated action of co-ordinately acting muscles. Hence even if it be true that cells in the motor cortex can be stimulated in so discretely localized a manner that overt movement in only one muscle results, it is still quite certain that in normal cortical activity no such small group of cells is ever in isolated action, but is activated always as a contributor in complex and widespread patterns of activity. Apply this to the small areas of cells of the frontal areas which have autonomic effects we may assume that none of these normally act in isolation: for example, that none of the numerous small cortical areas, from which a rise in blood pressure is produced by stimulation, are ever naturally in isolated action to produce a raised blood pressure and nothing else—we reject the idea of cortical blood pressure-raising centres. As Adrian (1947) well says—"the cerebrum is not concerned with the detailed administration of the body. It is concerned with long range objectives and with behaviour related to the outside world."

What, then, is the significance of these autonomic responses?

Fulton points out that while certain parameters of stimulation in the premotor area (Brodmann 6) produce co-ordinate movements of the opposite limbs and trunk other parameters applied in the same areas excite a dilatation of the vessels of the active muscles and constriction of visceral ones, thus ensuring the necessary increase of blood flow for muscles in activity.

He states that, in general, specific autonomic foci overlap with appro-

priate somatic areas and that the cortical map of the autonomic motor area is almost a replica of that of the somatic.

Bilateral frontal lobotomy has as its most striking consequence that change in emotional state called flattening or bleaching, a lowering of the tension of the affect, through which the beneficent effects arise and cause alteration of the patient's behaviour (Rylander, 1948). This alteration has been described according to the disposition of the observer as lack of initiative, loss of interest, tameness, loss of aggressiveness, docility, and even loss of soul.

Emotion is the immediate or remote promoter of all our activity. We are moved by emotion. Neurologically it might be regarded as a higher level built upon and above the neural substrate of co-ordinate action, and almost as ancient as it. Fulton's example of autonomic and motor functions subserving the same activity and lying in the same cortical area, might be applied further to the motor activity arising from emotion and the autonomic activity required for that motor activity to take place.

For emotion is not merely the prime mover, it is in its own evolution the outstanding mental state in which autonomic activities are manifest.

Our pupils do not dilate, our pulse does not strengthen and race, our breathing does not accelerate nor our muscles tighten when we contemplate a mathematical proposition but they do when we are angry, or humiliated or in love.

So we may well have the autonomic switches in our frontal cortex through which such effects may be mediated when our emotions are stirred.

When angry the animal fights. It is its frontal lobes that keep the muscles well supplied with blood, the pupils wide, the breathing deep, the hair erect, the face fierce, so that it may strike fear into its enemy and struggle long against him.

It is no transient reaction, it must be maintained by reverberating arcs as long as it is needed, and all the time the innumerable sensations of the autonomic activity are conveyed to consciousness and it is that complex of sensations that we call the affect of the emotion. It is not for nothing that we speak of our "feelings" in that sense.

I recall the James-Lange theory of the emotions—that emotion is, indeed, nothing but the sum of the bodily sensations which it arouses.

James (1892) says: "*Anger, fear, love, hate, joy, grief, shame, pride,* and their varieties, may be called the *coarser* emotions, being coupled as they are with relatively strong bodily reverberations.

"Our natural way of thinking about these coarser emotions is that the mental perception of some fact excites the mental affection called the emotion, and that this latter state of mind gives rise to the bodily

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expression. My theory, on the contrary, is that *the bodily changes follow directly the perception of the exciting fact, and that our feeling of the same changes as they occur is the emotion.* Common sense says, we lose our fortune, are sorry and weep; we meet a bear, are frightened and run; we are insulted by a rival, are angry and strike. The hypothesis here to be defended says that this order of sequence is incorrect, that the one mental state is not immediately induced by the other, that the bodily manifestations must first be interposed between, and that the more rational statement is that we feel sorry because we cry, angry because we strike, afraid because we tremble, sorry, angry, or fearful, as the case may be. Without the bodily states following on the perception, the latter would be purely cognitive in form, pale, colourless, destitute of emotional warmth. We might then see the bear and judge it best to run, receive the insult and deem it right to strike, but we should not actually *feel* afraid or angry."

By interpreting "bodily changes" as the autonomic responses associated with frontal cortical action we have arrived by a different path at the same point of view.

If as a result of lobotomy of both frontal lobes the autonomic functions of their cortex are abolished it would not be surprising if emotion, depending on such effects for the actuality of its affect, were bleached, and its appearance in consciousness but a ghost of itself, lacking all reality, all sense of urgency even though its cognitive aspects remain. The cause of the sorrow is still there but it no longer hurts—"I can't feel sad any more." No wonder the patient's relatives recognize the loss of warmth in the patient's emotions and say he has lost his soul!

My hypothesis, for what it is worth, is then that bilateral frontal lobotomy owes its main beneficial effect to the abolition of the wide sphere of cortically induced autonomic activity: that mental tension owes its unpleasant feeling-tone to this autonomic stress, is lessened when it is lessened, abolished when it is abolished.

When we recall that the anterior cingulate gyrus is said by Ward to have so much autonomic activity that it dominates the autonomic system we can understand how the dulling of the monkey's "feelings" resulting from the excision can cause its behaviour to change so much.

"Interest," too, has an emotional basis (without any emotions there would be no interests except those derived from the appetites) and so its impairment is explained by weakening of emotional feeling, there being no longer an afferent side to emotional driving force, and "aggressiveness" which is one of the effector aspects of emotion is impaired for the same reason. Loss of initiative, so often stressed as a consequence of bilateral frontal lobotomy, may also be traced in part to the lack of interest in

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tasks to be performed, to that lowering of tension which may be to the brain like a fall of voltage to an electrically driven machine.

(2) Hemispherectomy

When Dandy reported in 1933 the results of removal of the whole non-dominant hemisphere (except the basal ganglia) from two adults they were very much what might have been expected. He wrote then: "The only accurate and safe data concerning most cerebral functions can come from extirpation of parts of the human brain. From accurately defined and well-performed removals of this type the functional results if positive must be regarded as specific and if negative must exclude the part of the brain concerned from participation in the function tested. Nor can Broadbent's old theory that the corresponding part of the opposite hemisphere assumes their function be given even remote consideration. The arm, leg, and visual areas receive no such relief and losses of function due to injuries of the left hemisphere are not aided by any participation of the right." This quotation expresses the extreme view of fixed and specific localization of cortical function. It implies a set predestined functional arrangement of the cortex as precise and defined in all parts as it is in the visual area.

In the paper of Krynauw (1950) on hemispherectomy in cases of gross lesions of the brain, congenital or arising in early years, the results of the operation are very different from what one might have expected. The communication is a preliminary one, case reports are rather lacking in important neurological detail and follow-up has been very brief in several instances. A further communication is promised.

There are 12 patients ranging in age from 7 months to 21 years. 1 died after operation and in 2 the post-operative period was too short for assessment to be made. All but 2 had lesions dating from birth or within the first year, in 1 the lesion occurred at age 2, in one at 4½ years. The operation is described as removal of the affected hemisphere, with the exception of the thalamus, the caudate nucleus and its tail." The left hemisphere was the diseased one in 10 of the 12 cases but the results of operation show that it was never the dominant hemisphere. Hence gross disease from an early age in the left hemisphere seems to prevent the neurological organization of that hemisphere which determines dominance. The gross lesions involved in different cases the frontal, parietal, temporal or occipital lobes but one cannot deduce that such a lesion in any part of a hemisphere can prevent the establishment of dominant characters in it, for all patients had spastic hemiparesis and the inability to develop the motor powers of the hemisphere may have been the principal cause. As right-handedness must be largely structurally predetermined,

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the ability of the normally non-dominant hemisphere to assume the full organization of the dominant one when conditions require it is a testimony to the plasticity of cortical powers in infancy.

Before operation, most of the patients had fits, most were noisy, overactive and subject to violent outbursts of irritation and temper, and 9 were more or less grossly retarded in mental development. After operation the fits ceased in all cases, outbursts of temper and irritable conduct ceased in all cases where they had been present, the patient's emotional state becoming balanced and contented, and in 7 cases (all where the facts are recorded) the intellectual status improved. Children who had been unable to apply themselves to any task, unwilling or unable to learn, became after operation more intelligent, more interested, able to apply themselves and able to learn.

The possibility of such improvement is referred to by Penfield and Rasmussen (l.c., p. 201) who say: "The surgeon may even be forced to the paradoxical conclusion that brain removal has resulted in improvement of mental processes when the area removed contained a focus of epileptogenic discharge."

As most of these patients who showed such mental improvement had had fits before the operation and not after it, it may be that the intellectual retardation was partly due to the fits and, perhaps, to the use of sedatives in treatment; and the improvement after, to the cessation of these factors. This was not so in every case for improvement of the same degree occurred in a boy of 9 who had never had a fit, though he had been subject to violent bouts of temper, screaming, kicking and attacking those near him.

Another unexpected result was that after operation the hemiplegia had not usually become total though it was often worse for a time. In some cases it improved rapidly to the pre-operative level and occasionally beyond it. Athetosis and spasticity lessened in 3 cases.

In only one case is there any indication of disorder of the body image, of spatial orientation and other symptoms associated with disease of the parietal lobe of the non-dominant hemisphere. In that case, a boy of 10, there was a failure of appreciation of the relative position of the main elements of the design in drawing, and a tendency to mirror-writing. After the hemisphere had been removed in this case this symptom disappeared, his drawings were well orientated, and writing was normal. In all other cases hemispherectomy caused no disturbance of these functions.

Homonymous hemianopia and impairment of cortical modes of sensibility resulted from the operation. Aphasia was not present before or after operation.

It would appear, therefore, that organization of all higher cortical functions—the understanding and production of speech, orientation and body

scheme, emotional and intellectual functions can be maintained very well, if not perfectly, by one hemisphere, and *that* the one which would normally have been non-dominant. Only relatively low level functions—visual half-field absolutely and body sensation and Rolandic motor functions partially, seem tied to their own hemisphere and cannot be taken over by the other one, however early the lesion occurs.

It is not possible to say that the mental state of such hemispherectomized patients is ever as good as it would have been had the brain developed normally but we must conclude with Goody and McKissock (1951) that at birth "the brain stands ready for training" with powers of cortical adaptation much more plastic than we had thought. This adaptability persists though gradually decreasing as neural organization proceeds, and seems not to be entirely lost throughout life.

One other aspect of these observations is of great importance. The improvement in mental faculties noted after operation was associated with the cessation of discharges arising from the damaged hemisphere and impinging directly or by way of diencephalic mechanisms on the other hemisphere. Electroencephalograms were recorded before operation, and all showed gross dysrhythmias on both sides of the brain. After operation the EEG was normal in the remaining hemisphere, so that the discharging activity of the damaged hemisphere had not been, as it were, engrafted on to the rest of the brain. The buffeting of the diencephalic mechanisms and the opposite cortex had not turned these into discharging areas.

We have been accustomed to think that the effects of destructive lesions were due in part to the loss of function of the area destroyed and in part to the constructive effort of the brain to substitute for the lost function. In addition we were aware that some lesions especially cortical ones were liable to cause discharges of energy and so cause fits. We have known that extirpation of the diseased area might lead to cessation of fits but we would not have expected any general beneficial effect otherwise. So we were not prepared for the remarkable improvements in behaviour, intelligence, educability, etc., which have followed hemispherectomy.

When thinking of the effects of gross cortical lesions we must now remember not only the loss of function and the effects of compensation by the brain, but also the disorganizing effects of such lesions on the functions of the rest of the brain. One evidence of this is epilepsy which appears intermittently as a fit or some equivalent. But the *discharge* is not intermittent, it is continuous as is shown by the electroencephalogram, and its damaging effects on cerebral organization is probably due to that fact. It seems to be essentially of the same nature though less in degree in the periods between the fits as in the fits themselves.

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(3) Consciousness and the Highest Level

That lesions of the diencephalon often caused disturbances of consciousness has been recognized for many years.

All states of depression of the level of consciousness from mild lethargy to coma have been seen in tumours of the hypothalamus and special interest in the subject was aroused by the epidemic of encephalitis lethargica thirty years ago. A sleep-controlling centre was discussed and located by some in the hypothalamus and by others in the rostral part of the mesencephalon. In 1944 Jefferson emphasized that the sudden loss of consciousness in cerebral concussion must be due to the effect of the blow on the brain-stem and that the state of successive coma and drowsiness during recovery might be attributed to injury of lower centres. Meanwhile much work on the physiology of the hypothalamus had been carried out by Hess and by Ranson leading to the conclusion that sleep-controlling and arousal mechanisms were located in the posterior hypothalamus. Developments have been rapid in the past ten years. Moruzzi and Magoun (1949) have shown that stimulation of the brain-stem reticular system from the medulla up to the caudal part of the basal diencephalon suppresses synchronized rhythms in the cortex which when they are spread over the whole cortex are associated with loss of consciousness. They surmise that "a background of maintained activity within this ascending 'activating system' may account for wakefulness, while reduction of its activity either naturally, by barbiturates, or by experimental injury and disease, may respectively precipitate normal sleep, contribute to anæsthesia, or produce pathological somnolence."

Earlier Dempsey and Morison (1942, 1943) and Jasper (1947) and his co-workers have shown that thalamic stimulation produced generalized disturbances over the entire cortex. Hunter and Jasper (1949), by stimulating certain well-defined points in the intralaminar reticular system of the thalamus produced in the unanæsthetized cat attacks resembling *petit mal* and associated with widespread spike and wave activity in the cortex. When stronger stimulation was used a major epileptic seizure followed the minor one. Thus they established the presence of a diffuse projection system whereby electrical stimulation of the thalamus could produce universal synchronization of cortical activity, probably with loss of consciousness.

It may be added that Moruzzi and Magoun found evidence that their brain-stem reticular system probably acted on the cortex, in part at least, through Jasper's thalamic diffuse projection system.

It is possible that the manner in which electrical stimulation of these intralaminar thalamic centres causes cortical synchronization is by inter-

rupting the passage of the cortical activating stimuli from the brain-stem reticular system. Such interruption of normal function is familiar, as has been said, in electrical stimulation of the cortex. It may be that the intralaminar thalamic points in question are normally forwarding systems for the impulses arising in the reticular area, i.e. normal function of arousal.

This possibility is strengthened by the fact that when Moruzzi and Magoun applied their 300 cycle per second stimuli to the same points in the thalamus from which Jasper produced synchronization in the cortex with stimuli at 1 to 60 cycles per second, they produced not synchronization but activation and the abolition of synchronized rhythms.

Synchronization of electrical activity of cortical cells producing high voltage rhythms is associated with the resting state (Adrian, l.c., p. 75) and is replaced during normal activity of the cortex by a differential low voltage activity not detectable by the electroencephalograph. This is, of course, shown in the effect of visual stimuli in abolishing the alpha rhythm from the occipital cortex. But we must no longer regard such abolition as the result of sensory stimulation, it is rather a function of that aspect of consciousness which we call attention. The visual stimulus which is not attended to has little effect on alpha rhythm, if it were possible to be unconscious of it, it would probably have no effect at all. The really important fact is that a voluntary action of the mind, namely attention to a stimulus, has an observable physical effect—namely arrest of synchronized cortical (alpha) rhythm and the substitution of differential cortical action.

Synchronized rhythms at slower or faster rates than the alpha rhythm may occur, like the alpha rhythm itself, over small or large areas of the cortex without any noticeable affection of consciousness but when universal over the cortex consciousness is lost. Adrian says (l.c., p. 79): "What seems to be necessary (for the mind to function) is that there should be differential rather than uniform activity in some part of the cortical area, though not necessarily in a very large part." Synchronized rhythm over the whole cortex characterizes natural sleep and barbiturate anæsthesia.

It is the appearance of such universal synchronized rhythms that results from intralaminar thalamic stimulation and their prevention or abolition by stimulation of the brain-stem reticular system.

From all this and much other work we should, I think, accept that brain-stem, hypothalamic, and thalamic mechanisms can when stimulated electrically or damaged have effects on the cortex as a whole, producing on the one hand universal synchronization of activity associated with unconsciousness or on the other the differential activity associated with consciousness.

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We cannot cause loss of consciousness either by stimulation or excision of any limited area of the cortex, unless the stimulation is strong enough to cause generalized convulsions. Foci discharging in the cortex produce local synchronization of rhythm without affection of consciousness and the discharge may spread and intensify over the cortex still without loss of consciousness until it becomes generalized (Jasper, 1949), and there is then evidence that generalization results from the spread of discharge to diencephalic mechanisms whereby cortical universalization and loss of consciousness are both brought about (Penfield and Jasper, 1947).

Large areas of the cortex, too, may be excised in man under local anæsthesia without noticeable affection of consciousness.

Such consideration of cortical impotency and of diencephalic potency to affect consciousness have led to the conception that diencephalic mechanisms control the cortex and are thus the highest level of cerebral function, a level which Hughlings Jackson himself surmised might be located in the frontal cortex.

Penfield especially has championed this theory and has cited numerous clinical experiences pointing to a diencephalic location for the neural substrate of consciousness. The theory propounded may be indicated by some quotations. Speaking of the dorsomedial nucleus of the thalamus he says: "We may consider the possibility that this portion of the thalamus, or other areas in the diencephalon most closely related to it, contains the essential neuronal mechanism upon the integrity of which depends the very existence of consciousness, a mechanism which is able to employ the anterior frontal regions in the process of thinking and to use them in the elaboration of thought" (Penfield and Rasmussen, 1950, p. 227). In reference to epileptic automatism he states that the discharge "has affected the grey matter" (i.e. the diencephalic grey matter) "that constitutes a higher level of integration than the cerebral cortex" (Penfield, 1949). It is true that he also states: "It seems fair to conclude that within the diencephalon there are neurone circuits which may be considered the highest level of neuronal representation and re-representation. But much of the function at this level is made possible and is elaborated by the special areas of the cerebral cortex. It is, therefore, inaccurate to say that the cortex belongs to a lower level of activity (Penfield and Rasmussen, 1950, p. 235).

I could accept the latter part of this statement but it seems to me to conflict with the rest, which appears to go beyond the facts of brain-stem and diencephalic function in relation to cortical activity mentioned above and those facts which Penfield relates from his own experience. Even though it is agreed that cortical activity can be controlled by discharges from the lower neurone circuits and that consciousness may be thus

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abolished it is still the cortex upon which they act to produce this effect. Even though large areas of cortex can be excised without loss of consciousness, consciousness would be unthinkable without a cortex. It could have no content.

Consciousness is that quality by which the mind is aware of what is going on in it. It can vary in quantity so that mental processes can be sharp and distinct or dull and blurred. Mental processes can be brought, as it were, to a focus so that the field of mental activity is intense but only at the expense of being narrowed down. This process we call attention. We can submit the whole possible range of mental content to this process in successive efforts of attention but we cannot attend to everything at once. That which we attend to is the *content* of mind, the process of attending to some part of the content of mind is the concentration of consciousness on that part.

It is essential to avoid confusion of these terms—"consciousness" is not synonymous with "mind," though one cannot, I think, be conscious without being conscious of something, but the mind certainly extends beyond consciousness and extra-conscious processes certainly influence what is, and is to become, conscious.

It must be realized, however, that the content of mind varies with the intensity of consciousness. In low states of consciousness, as in falling asleep or in delirium, mental content is small, vague, and illogical, and it cannot become otherwise without an increase in the intensity of consciousness.

A crude simile would be to liken the mind to a vast picture which is illuminated by consciousness. When the light is low the details are obscure, when it is bright they are better seen; and attention is like a bright beam of light that we direct now here now there to see the details more clearly. But the meaning of the picture, its significance, is not in the light. It may even be said to persist when there is no light, just as the mind retains its integrity through the periods of unconsciousness we pass in sleep. It follows that neural processes on which the level, or even the existence, of consciousness depends are not necessarily the same as those which serve processes of thought or re-representation. The role of the thalamic, hypothalamic, and brain-stem mechanisms we have been considering is in some way to control the quantum of consciousness through their control of cortical activity, to raise or reduce the intensity of that activity quantitatively; under certain conditions to allow it to fade into rest, under others to activate it but never to determine what will be the outcome, the product of such cortical processes.

They may as it were turn the tap on or off but are not responsible for the kind of liquid that flows from it. Diencephalic activity is a coarse

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activity, not quite "all or none" but producing modulation only through its effects on more specific cortical mechanisms.

Language, emotional feeling, spatial perception are cortical functions dependent on complex integrations and belong to the highest level of function. The fact that they may be brought to an end by a process arising elsewhere does not constitute that process a higher one than they. An electrically driven machine can be stopped by turning off the current but the current is only a necessary fuel; it cannot do the work the machine is built to perform except by driving it. It would similarly be possible to think of the activity of these lower circuits as being necessary to the cortex by supplying it with some stimulus, some neural energy which it needs and without which it might not be active at all. This would sufficiently explain the indispensable character of the work performed by such lower mechanisms without dethroning the cortex or some parts of it from its undoubted place at the top of all neurological levels. Throughout the nervous system complexity of organization and elaborateness of function increase from lower to higher levels. Which is it more correct to regard as the highest level, consciousness which the lower animals certainly have, or the richness of intellectual and emotional life which is the privilege of man alone?

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INTELLECTUAL IMPAIRMENT WITH LOCALIZED CEREBRAL LESIONS

BY

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I. Introduction

Since the observation that disturbances of language are related to lesions of the dominant hemisphere, neurology has included a number of "intellectual" disturbances among the localizing signs of cerebral lesions. There remains, on the other hand, a large body of opinion which maintains that intellectual ability is a unitary function, and is only depressed to the extent that the lesion affects the activity of the brain as a whole: an opinion which has derived considerable support from Lashley's (1929) significant monograph demonstrating the "equipotential" nature of cerebral activity in the rat. But, discussing the application of his findings to the interpretation of human cerebral function, Lashley observed (Ch. X) that "in the whole literature of neurology there is scarcely an attempt to measure the actual capacity of a patient with brain injury to perform such a varied assortment of tasks as is included in a modern intelligence test." Since 1929, however, a number of studies has been reported in which standardized tests have been used on neurological patients.

Perhaps the least consistent results have been obtained from examinations of patients with frontal lobe lesions. German and Fox (1934) presented two cases of frontal lobectomy for glioma, and from the specific impairment which resulted, concluded that "the intellectual defect appeared to bear a relationship to cerebral localization and dominance rather than to cerebral mass." Brickner (1934, 1939) reported a careful post-operative study and seven-year follow-up of a case of bilateral frontal lobectomy, and in his interpretation of the case claimed that the underlying disability was "loss of the function of synthesizing intellectual units." Ackerly (1935) studied a woman with bilateral damage who, two years after operation, achieved a normal score on the Stanford Binet (largely

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verbal) intelligence test, but did poorly on a performance test: after discussing the features of her performances, he concluded that she was unable "to take in simultaneously the elements of a setting."

Following the particular claims of Goldstein (1936), some studies have been made of the effect of frontal lesions on the performance of tests involving abstraction: Nichols and Hunt (1940) noted a deficit in this field in a case of partial bilateral frontal lobectomy, an observation supported by Halstead (1940) and Halstead and Settlage (1943) in the performance of groups of patients with localized lesions on various sorting tests.

Lidz (1939) described a patient tested before and after right frontal lobectomy for a glioma in that situation. Essentially, a battery of tests revealed no change: his I.Q was the same before and after operation; but there was a noteworthy fall in his score on a test of inferential reasoning. Later the same author (Lidz, 1949) presented the results of a variety of tests on a case of left prefrontal vascular accident: he found that the patient had particular difficulty in performing tests requiring consideration of alternative or simultaneous approaches, or shifting from one approach to the other.

The most detailed study of a group of patients with frontal lesions is that of Rylander (1939) in which he examined 32 patients who had had operations on a frontal lobe, and compared the results with those of an equal number of carefully chosen controls. The patients were significantly poorer than the controls in the majority of performances, though not on the simpler tests of attention, immediate memory span, calculation, and recall of a story. They were slower on timed tests; learning was slightly impaired; and particularly tests of grouping according to abstract principles, and one of arranging pictures to tell a story, were poorly done by the patients. There appeared to be no difference between the effect of left and right-sided lesions, but there was a relation between the degree of impairment on tests and the amount of frontal tissue removed.

The foregoing investigations suggest, then, a pattern of intellectual impairment common to cases of frontal lesion. But there has also been a number of studies in which the expected changes have not been found. Thus, Penfield and Evans (1934, 1935) presented 3 cases of frontal lobectomy, in which the only post-operative deficits reported were, in one case, "loss of power and initiative"; and in another, slightly reduced immediate memory span for digits and difficulty with mental arithmetic. Again Hebb (1939, 1941, 1945) found little evidence of intellectual impairment in a series of cases with unilateral and bilateral frontal ablations, and considered that the evidence opposed any localization of "what intelligence tests test" in the frontal association areas; that the "synthesis" type of

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theory of Brickner and others was inadequate to explain all the deficits in their patients; and that Goldstein's concept of loss of abstraction was "vague and inconclusive." Jefferson (1937), discussing the inconstancy of symptoms resulting from similar frontal lesions, concluded that "the brain must function intellectually and emotionally as a whole, . . . rather than in the departmental way that anatomical research once suggested."

With post-centrally located lesions, on the other hand, the results of intellectual testing have been less equivocal, and may be subdivided into the studies associated with aphasia, and those associated with other "higher" deficits, as summarized by Critchley (1949). The first extensive use of accepted intelligence and ability tests was in the study of 60 aphasic patients reported by Weisenburg and McBride (1935), from which their general conclusion was that language intelligence scores were lower in the "receptive" group of patients, with predominantly post-central lesions. Non-language test scores, however, did not suffer similarly, while it appeared that they were impaired in the control cases with right-sided lesions, in whom language functions were intact. Similar results were noted by Fox and German (1935) in their study of a case of left temporal lobectomy: the mild dysphasia was accompanied by a fall in achievement on a language intelligence test, while non-language performance was unaffected. Their patient showed also particularly impaired retention of auditory speech material, a point emphasized in a study of verbal learning in aphasia by Zangwill (1946); while Benton (1945) demonstrated that retention of non-verbal material might be well preserved in dysphasia. Again Schiller (1947) in a careful study of 100 traumatic aphasics, using Raven's Matrices as a test of intelligence, found that impairment in aphasics was most marked with temporo-parietal lesions.

Apart from aphasia, the deficits most significantly related to intellectual performances have been grouped by Critchley according to their occurrence with lesions in the dominant, non-dominant, or both hemispheres. Thus acalculia is associated with lesions in the dominant parietal region; constructional apraxia is attributed to lesions in either hemisphere; and "agnosia for extra-personal space" to lesions on the non-dominant side. Fox and German's case of left temporal lobectomy showed a considerable drop on a standardized test of mathematical ability. Kennedy and Wolf (1936), in their review of intellectual defects in aphasia, noted impairment of arithmetical ability; while Weisenburg and McBride, on the other hand, found that performances on mathematical tests were more impaired in their control cases with right-sided lesions. Acalculia also forms an integral part of the syndrome described by Gerstmann (1940), which is characteristically associated with a dominant posterior parietal lesion; and Schiller found calculation most severely impaired in his patients with

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posterior lesions—patients who showed also the most marked impairment on a constructional intelligence test (Kohs' blocks). Constructional apraxia has also been related by Mayer-Gross (1936, 1938) to the presence of a predominantly left parietal lesion.

Constructional disabilities associated with right-sided post-central lesions are, however, related to disturbance of spatial perception rather than to a primarily apraxic disorder. Penfield and Evans (1934) described a patient in whom right temporal lobectomy resulted in an impairment of distance judgment: while Weisenburg and McBride found that their control patients with right-sided lesions showed more disability on tests involving visual-spatial performance than did the normal controls. More recently McFie, Piercy and Zangwill (1950) have described a group of patients with lesions of the right post-central region, in whom the presence of visual-spatial agnosia resulted in impairment not only on a constructional intelligence test (Kohs' blocks) but also on purely perceptual tests, such as Raven's Matrices.

It is relevant at this point to consider the evidence for the subdivision of "intelligence" which has accumulated as a result of testing groups of normal subjects: here again we find the same difference of opinion as noted above, between the "unitary" view of intellectual ability, and the view that it is composed of a variety of intellectual abilities. Spearman (1932) claimed that the intercorrelations observed between almost all tests involving any sort of intellectual function could be accounted for mathematically on the basis of a single function common to all the tests of intelligence. Memory tests alone did not satisfy the mathematical criterion; and "retentivity," he held, was an altogether different process from intellection. Following Spearman's description of his mathematical technique, a great number of psychologists and mathematicians have approached the problem of intellectual organization using Spearman's method and other, more elaborately mathematical, techniques, known as "factor analysis." Thus Thurstone placed chief emphasis upon the importance of "group factors," and his technique of analysis is designed primarily to extract these factors. In a study (1941) of over 1,000 school children with 60 tests, he demonstrated that the intercorrelations between results could be ascribed to the operation of a number of well defined factors, named, on the basis of the test material, Verbal, Space, Number and Memory; and some less clearly defined factors, including two apparently associated with Inductive and Deductive Reasoning. At the same time, his results showed that these primary factors were highly intercorrelated among each other, suggesting the operation of a "general" factor, like Spearman's "g," but that Memory correlated poorly with the

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others. Elsewhere Thurstone (1948) has suggested that aphasia may selectively damage the operation of verbal factors.

Further work on the relationship of these factors led Spearman and Wynne Jones (1950) to accept the evidence for verbal and spatial group factors, but they continued to stress the importance of "g." Arithmetical ability, they claimed, seems to be related only to "g," but "computation seems to be an independent faculty" (p. 145). Vernon, in his review (1950) of factor analysis, found that the evidence supported a "hierarchical" view of intelligence: that is, with an overall general factor, subdivisions of abilities under group factors (such as verbal, spatial, etc.), and specific abilities related to each test.

Before proceeding to discuss criticisms of the "departmental" view of intellectual activity, it must be noted that one significant study has appeared in which both neurological and psychological theories of intellectual organization have been considered. This, reported in Weisenburg, Roe and McBride's "Adult Intelligence" (1936), was an extension of Weisenburg and McBride's study of aphasia. In the course of this investigation 85 normal subjects, 60 patients with left-sided lesions resulting in aphasia, and 22 patients with comparable right-sided lesions, were given a large battery of standardized psychological tests. The individual normal subject, whether of higher or lower intelligence, generally maintained a consistent level throughout his test performances ("particular constellations of abilities . . . are the exception rather than the rule," p. 81); but analysis of the correlations between test results showed interrelationship among the language tests, a slight relationship between these and arithmetic scores, and very little relationship between language and non-language tests. Turning to the performance of the groups of patients (p. 129) "the evidence for a distinction between different groups of mental abilities gains additional support from the findings for the pathological groups studied by the same tests. Cases of right-sided cerebral lesion without aphasia . . . were found to be significantly inferior to the normal only on the arithmetic and some of the non-language tests," while "only a few aphasic patients have anything like as great difficulty in non-language as in language work." An exceptional result was noted in their Analogies test, a verbal test whose scores and sensitivity to impairment were more closely related to non-language tests and to right-sided lesions than were the other verbal tests. The authors concluded that (p. 129) "there are in all probability more or less independent groups of mental abilities. The typical normal adult does not show great differences in the development of these abilities. . . . In cases of brain disease, however, or at least in cases of localized brain disease, they may be affected unequally." The differential effects of right- and left-sided lesions agree precisely with those propounded

some sixty years earlier by Hughlings Jackson (1874) in his analysis of the dual nature of cerebral function, in which he stated that there were two "series" of central processes in intellection, the "audito-articulatory" and the "retino-ocular," and that damage to the left hemisphere would disturb the voluntary (or "propositional") aspects of the former, resulting in aphasia; while damage to the right hemisphere would interrupt the voluntary aspects of the latter series, resulting in "imperception."

Vigorous opposition to the subdivision of intellectual functions has come from the "unitary" school: and here an outstanding position is taken by Goldstein, by virtue of his distinction between the "abstract" and the "concrete" attitudes. In an experimental study of these aspects of behaviour, Goldstein and Scheerer (1941) define these attitudes as "capacity levels of the total personality." The abstract attitude, in their view (p. 4), embraces more than the "real" stimulus in its scope; it enables the subject to detach himself from his experiences, to account for his performance, to hold in mind simultaneously various aspects of the stimulus and to shift from one aspect to another, to analyse and synthesize, to learn, to form concepts, and to plan. All this is disturbed by a cerebral lesion, which leaves the patient with only the limited approach of the concrete response, which is "realistic," unreflective, and never mediated by discursive reasoning. For Goldstein, the localization of a lesion is not relevant to its intellectual effects: disturbances in speech, and in non-language performances, "are simply the effect of the same dedifferentiation of brain function in two performance fields." "To speak of the condition of intelligence in aphasic patients in general—its maintenance or deficit—is impossible" (Goldstein, 1948, p. 117).[1] This aspect of the theory is not, however, easy to criticize on the basis of the evidence presented by Goldstein and Scheerer, as there is no mention of the location of the lesion in any of the patients studied. In view of the fact that many other authors have claimed specific effects for circumscribed lesions, there can be no justification for assuming, *a priori,* an "anti-localization" approach of this type; although a number of the tests devised by Goldstein and his associates have considerable clinical interest.

More precise support for the "unitary" view of intellectual organization has come from the field of comparative psychology, in which the work of Lashley (1929) has had the greatest theoretical influence. From an extensive series of experiments, his chief conclusion was that the degree of impairment of maze-learning in rats was proportional to the extent of

[1] Students of "intelligence theory" will, however, recall the various definitions of intelligence which have been proposed (summarized by Sherman, 1945). Goldstein's extensive definition of "abstract attitude" includes a great number of these; and it may be that loss of "abstract attitude" is in fact simply a loss of what other workers have called intelligence.

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cortical surface ablated, and unrelated to the locus of damage. Reviewing the clinical evidence then available, Lashley also concluded (Ch. X) that there was little evidence of any difference between the nature of cerebral organization in man and in the rat.

Although Lashley has since then modified his view from one of equipotentiality of the entire cortex to one of regional equipotentiality, or "functional equivalence of parts within a specialised area" (Lashley, 1933), his earlier work still exercises a considerable influence; and it is relevant to recall certain criticisms foreshadowed by himself. Lashley has taken, and continues to take (e.g. 1949), the view that intellectual capacity consists largely of learning and, conversely, that learning involves "problem-solving" abilities; but he wrote (1929, p. 14) "capacity to memorize has shown but low correlations with intelligence, measured by other criteria; and, to the extent that our studies of learning in animals are what they have purported to be, measures of mnemonic capacity, they are irrelevant to the problem of intelligence." We may recall that Spearman and Thurstone both found, from statistical studies, that retention tests showed little relation to other intelligence tests. From clinical studies, there comes confirmation of the view that retention is a function dependent on the integrity of the whole cerebrum.[1] This was explicitly stated by Kolodny, after studies (1928, 1929) of patients with frontal and temporal lesions: "one gains the impression that memory is much more a function of the brain as a whole than of any specific area." Memory impairment remains a constant feature of all types of dementia (Critchley, 1933); and at the same time is the most frequently observed mental deficit in studies of cases with circumscribed lesions, irrespective of localization, as in the study of 662 patients with localized lesions by Busch (1940). And here it may be remarked that Busch found no correspondence between the incidence of symptoms and the presence of raised intracranial pressure in his very considerable series of patients.

II. Examination

The foregoing review of studies of organic intellectual impairment suggests a general hypothesis for examination: *that intelligence is composed of more or less independent abilities or groups of abilities, which are selectively impaired by circumscribed lesions in different locations.* It suggests, moreover, that the particular abilities for investigation should

[1] It is interesting to note that in fact the integrity of the thalamus may be more fundamental to retention than integrity of the cortex: Lashley's (1944) experiments with fine cortical lesions showed a surprisingly high correlation between impaired learning and extent of thalamic lesions; and Smyth and Stern (1938) reported 4 cases of intrinsic tumour of the thalamus in which only "non-specific" features of dementia were apparent.

include ones which may be described as "memory," "abstraction," "verbal," "numerical," and "visual-constructive"; and that, as far as localization of the lesions is concerned, laterality and subdivision into the conventional lobes should provide sufficient evidence for or against the hypothesis.

The comparison, in any individual subject, of a number of descriptively different intellectual operations, has been made possible by the Bellevue Intelligence Scale (Wechsler, 1944). In this scale, the scores on individual subtests are rendered comparable in terms of "equivalent weighted scores"; and the standardization includes corrections for the differential changes found on each subtest with normal ageing. In the present study, those subtests were selected which were relevant to the problem under consideration: and some additional tests (of retention and of abstraction) were included in the scheme of examination. Where necessary, a method of standardization of these tests was developed and is described below.

The different abilities investigated, with the corresponding tests, completed by most patients, were as follows:

A. *Premorbid intelligence.*—This was estimated on the Vocabulary and Picture Completion subtests of the Bellevue Scale, which have been found to be relatively insensitive to organic deterioration (the latter subtest involves identification of missing features in 15 small pictures).

B. *Retention.*—(*a*) *Retention of verbal material* was tested on Digit Span, forward and backward; and on rote learning of the "Babcock" sentence and of a series of digits one longer than the forward span (Zangwill, 1943).

(*b*) *Retention of visual material* was assessed on the "Memory for Designs" item of Terman and Merrill (1937). This was drawn by the examiner, and exposed for as long as the patient wished before he attempted the reproduction from memory.

(*c*) *Wechsler's estimate of deterioration.*—This is derived, by Wechsler, by comparison of Vocabulary, Picture Completion, Information, and Object Assembly scores (less sensitive to organic deterioration) with Arithmetic, Block Design, Digit Span, and Digit Symbol scores (more sensitive to deterioration). In the present study two of the "insensitive" subtests have been omitted.[1]

C. *Other abilities.*—(*a*) *Abstraction,* dealing with non-verbal material, was examined on Weigl's Colour-Form sorting test (Goldstein and Scheerer, 1941). This was scored simply as "pass" or "fail," on the basis of the patient's ability to sort the pieces both by form and by colour.

(*b*) The *verbal* test used was the Similarities subtest of the Bellevue

[1] Information contains too many items unknown to English subjects: Object-Assembly is particularly sensitive to visual-constructive disabilities (cf. Allen, 1947).

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Scale, which involves the description of a similarity between certain pairs of words (e.g. Orange and Banana). It has the disadvantage of involving also, from a logical point of view, the process of abstraction.

(*c*) *Numerical* ability was assessed on the Arithmetic subtest of the Bellevue scale, with currency denominations changed to English coinage.

(*d*) *Visual-constructive* ability was assessed on the Block Designs subtest, a shortened version of Koh's block designs.

(*e*) It was found that the results of those patients who did the Picture Arrangement subtest were sufficiently interesting to warrant their inclusion.

III. Analysis of Results

The 58 cases whose test results are examined include all the patients referred to us for psychological examination over a period of two years, who were right-handed, in whom a sufficient part of the series of tests was completed, and for whom there was considered to be sufficient evidence of a localized lesion. Their test results are collected in the appendix, while Table I summarizes their ages and the nature and location of their lesions.

To test the hypothesis under consideration, the general scheme of the analysis has been to group the results according to the laterality of the lesion, and where there appeared to be a difference in the mean scores, to apply the appropriate statistical test for the significance of this difference. Where the difference appeared to depend upon localization of the lesion within the hemisphere, this effect was again examined for its statistical significance. Where possible, the relation between size of lesion and test results was also considered.

(1) *Retention.*—Table II indicates the estimated extent of the lesion, the presence of raised intracranial pressure, and compares the results on the retention tests and on Wechsler's deterioration score, for those 44 of the patients for whom adequate data were available.

It is not, of course, possible to rank the patients in order of size of lesion, but we have, on the basis of operative or radiographic evidence, subdivided the cases into a group with evidently small lesions (S) and those with large lesions (L): 14 patients could not be classified on this basis. The criterion for increased intracranial pressure was the finding of papilloedema. In order to enable the summation of the results of the retention tests, these have been converted into "equivalent" scores, on the basis of their distribution in the whole series of patients: these values are given at the foot of the table. The final column represents the total of these equivalent scores for each patient: where tests had not been completed, the mean of the other scores was substituted.

These results have been analysed under the following headings, higher "scores" representing greater impairment:

TABLE I.—AGE, SITE AND NATURE OF LESIONS

(Hospital Record Number in Parentheses)

Case	Age	Lesion
		Left Frontal
1	36	Meningioma (12461)
2	44	Meningioma (13136)
3	43	Glioma (13885)
4	35	Meningioma (14712)
5	44	Glioma (15613)
6	56	Glioma (16172)
7	51	Vascular accident (16673)
8	39	Glioma (23863)
9	20	Glioma (24968)
10	34	Cortical laceration (26715)
11	16	Shrapnel wound (3647)
		Right Frontal
32	43	Glioma (11980)
33	31	Amputation (11241)
34	46	Meningioma (9938)
35	41	Lobectomy (13148)
36	43	Atrophy (12204)
37	41	Meningioma (15605)
38	48	Lobectomy (11574)
39	37	Porencephaly (484)
40	58	Meningioma (17310)
41	50	Meningioma (20920)
42	30	Glioma (22601)
43	41	Tumour (22681)
44	56	Glioma (23439)
45	27	Amputation (23559)
46	28	Glioma (27179)
47	51	Lobectomy (25687)
		Left Parietal
12	23	Porencephaly (548)
13	31	Vascular accident (9720)
14	43	Meningioma (13234)
15	52	Vascular accident (16601)
16	46	Atrophy (18575)
17	47	Meningioma (19040)
18	60	Meningioma (19013)
19	61	Vascular accident (17956)
20	20	Glioma (17716)
21	21	Porencephaly (9411)
22	43	Glioma (20727)
23	29	Glioma (21490)
24	64	Meningioma (20847)
25	56	Angioma (22907)
26	22	Abscess, excised (25065)
		Right Parietal
48	55	Meningioma (3130)
49	55	Glioma (9140)
50	47	Meningioma (12592)
51	46	Carcinoma (12876)
52	53	Tumour (15297)
53	52	Meningioma (15249)
54	47	Meningioma (16679)
55	47	Glioma (21172)
56	16	Meningioma (22139)
		Left Temporal
27	51	Abscess (12926)
28	36	Calcification (76)
29	35	Tumour (1680)
30	42	Tumour (8375)
31	26	Focal epilepsy (9671)
		Right Temporal
57	24	Shrapnel wound (11315)
58	36	Glioma (13891)

(a) "Verbal" retention: Although the means of the "scores" for digit learning with left- (1·2) and right- (1·7) sided lesions are not significantly different, the mean "scores" for learning the Babcock sentence, 2·1 for left-sided and 1·2 for right-sided lesions, are significantly different at the $p = < 0{\cdot}05$ level ($t = 2{\cdot}4$).

(b) "Visual" retention: The Memory for Designs test was failed by 10 out of 26 patients with left-sided lesions, and by 17 out of 25 right-sided patients: this difference, with a χ^2 of 5·3, is significant at the $p = < 0{\cdot}05$ level.

(c) Wechsler's estimate: The mean "score" for left- and right-sided lesions is the same (1·1).

(d) Total score: The mean of this "score" for the cases with estimated large lesions is 6·3, and for those with small lesions 4·3: this difference, with $t = 2{\cdot}2$, is significant at the $p = < 0{\cdot}05$ level. The means for those with evidence of raised intracranial pressure (6·4) and those without (5·4) are not significantly different; nor are the means for those with left-sided (5·4) and right-sided (5·9) lesions.

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TABLE II.—GENERAL IMPAIRMENT

"Equivalent scores" calculated as follows:

Digit learning: 2 repetitions, 0; 3 repetitions, 1: 4 and 5, 2; 6 +, 3.

Babcock Sentence: 2 and 3 repetitions, 0; 4 and 5 repetitions, 1: 6–8, 2; 9 +, 3.

Memory for Designs: passed, 0; failed, 3.

Wechsler's "deterioration loss": 0–19%, 0; 20–29%, 1; 30–39%, 2; 40% +, 3.

Case	*Size of lesion*	*Raised intra-cranial pressure*	*Digit learning*	*Babcock sentence*	*Memory for designs*	*Wechsler's deterio-ration*	*Total score*
1	L	+	1	2	0	0	2
2	L	+	—	3	3	2	10·7
3	L	0	3	3	0	2	8
4	L	+	2	3	0	1	6
5	L	+	2	3	—	2	9·3
7	S	0	0	1	0	1	2
8	L	0	0	0	0	0	0
9	L	0	0	—	3	3	8
10	S	0	2	3	0	0	5
13	S	0	0	0	—	2	2·7
15	L	0	3	3	3	2	11
17	S	+	0	0	0	0	0
18	L	0	2	3	3	3	11
19	S	0	2	3	3	0	8
20	L	0	0	—	3	3	8
23	L	+	1	1	0	2	4
24	L	0	1	—	—	0	2
25	S	0	2	—	3	1	8
26	L	0	1	1	0	1	3
27	S	0	1	3	0	0	4
28	S	0	1	2	3	0	6
29	S	0	0	3	0	1	4
30	S	0	2	3	0	0	5
31	S	0	—	0	0	0	0
32	L	0	1	—	3	0	5·3
33	L	0	—	2	0	0	4
34	L	0	2	0	3	0	5
35	L	0	3	0	3	1	7
37	L	0	1	2	0	0	3
38	L	0	1	—	0	0	1·3
39	L	0	3	—	3	2	10·7
40	L	0	2	—	0	1	4
41	S	0	0	0	3	1	4
43	L	+	2	—	3	2	9·3
44	L	0	2	—	3	1	8
45	S	0	3	—	0	2	6·7
46	L	0	3	1	—	2	8
47	L	0	2	1	0	0	3
48	L	+	—	1	3	3	9·3
49	L	0	—	0	3	3	8
51	L	+	2	3	3	1	9
52	L	+	—	2	3	—	6·7
54	S	+	0	0	3	1	4
57	S	0	0	0	0	0	0

Statistical analysis therefore indicates that, taking all the tests together, impairment on tests of retention is significantly greater with the large than with the small lesions, but that it is not significantly greater in the cases of raised intracranial pressure. Nor is it significantly greater with lesions of either hemisphere, though individual tests show a differential sensitivity according to the perceptual material involved—thus verbal learning is

more impaired with a left-sided lesion, and retention of visual material with a right-sided lesion.

(2) *Individual abilities.*—Table III summarizes the impairment in each case of sorting, verbal, numerical, visual-constructive, and "picture arranging" abilities, as represented by Weigl's test and the Similarities, Arithmetic, Block Designs and Picture Arrangement subtests of the Bellevue scale. The table records the presence of dysphasia, constructional apraxia and visual-spatial agnosia as evident on clinical examination: in parentheses after the Picture Arrangement column is indicated the number of pairs of cards in this test incorrectly left by the patient in the order presented by the examiner.

The method adopted for calculating impairment on the particular subtests of the Bellevue scale is as follows: (*a*) the mean score on subtests not sensitive to organic impairment (Vocabulary and Picture Completion) is taken as representing the patient's pre-morbid level; (*b*) from this is subtracted the score on the subtest under consideration: this figure represents the total degree of impairment, which is (*c*) corrected for age by subtraction of the values given by Wechsler (1944, p. 222) and Fox and Birren (1950)

(*a*) *Abstraction:* 8 of the 30 cases with left-sided lesions failed Weigl's test, and only 1 of the 25 with right-sided lesions. This difference is, however, too small to stand up to statistical tests of significance.

(*b*) *Verbal:* The mean loss on the similarities test is 2·7 points with left-sided lesions, and 0·5 with right-sided lesions. This difference is significant at the $p = < 0{\cdot}01$ level ($t = 3{\cdot}5$). This difference remains even if the cases with dysphasia are excluded from the calculation: the mean loss in cases of left-sided lesion without dysphasia is 2·5 points, which differs significantly from the right-sided mean (0·5) at the $p = < 0{\cdot}01$ level ($t = 3{\cdot}1$). The slightly higher value of the mean loss for the dysphasics (3·1) is not significantly different from that of the left-sided non-dysphasics (2·5). At the same time, the mean losses with left frontal lesions (1·7) and left parieto-temporal (3·3) lesions are "suggestively" different ($t = 1{\cdot}7$, $p = < 0{\cdot}1$).

(*c*) *Numerical:* The difference between the mean losses on the Arithmetic subtest with left (3·7) and right (2·2) lesions is not significant; but the mean loss for the left parietal lesions alone (5·4 points) is significantly greater than that for the cases with lesions in all the remaining situations (2·2), with $t = 3{\cdot}4$ and $p = < 0{\cdot}01$. The difference in impairment between cases with dysphasia (4·6) and left-sided cases without dysphasia (2·5) is not significant.

(*d*) *Visual-constructive:* Mean losses on Block Designs are significantly greater with right- (2·8) than with left-sided (1·1) lesions ($t = 2{\cdot}3$, $p = < 0{\cdot}05$). In each hemisphere, parietal lesions are associated with significantly greater impairment than are frontal lesions: right parietal 4·6 *vs.* right frontal and temporal 1·9 ($t = 2{\cdot}4$, $p = < 0{\cdot}05$); and left parietal 2·1 *vs.* left frontal and temporal 0·1 ($t = 2{\cdot}3$, $p = < 0{\cdot}05$). At the same time right parietal lesions are associated with significantly greater impairment than are left parietal lesions ($t = 2{\cdot}8$, $p = < 0{\cdot}02$).

(*e*) *Picture arrangement:* Impairment on this test is significantly greater with right-sided lesions (4·1 points) than with left-sided ones (1·8 points), at the $p = < 0{\cdot}01$ level ($t = 3{\cdot}1$). The difference between mean impairment with right frontal (3·8) and left frontal (1·8) lesions is only at the "suggestive" level ($p = < 0{\cdot}1$): there is, however, an indication of a qualitative difference in performance in these two groups, shown by the greater incidence of cards left in their original order in cases of right frontal lesion (the patients nevertheless inventing plausible stories to suit these sequences).

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TABLE III.—IMPAIRMENT ON SORTING TEST AND ON SUBTESTS OF THE BELLEVUE SCALE

Under "Disability", D signifies dysphasia; C, constructional apraxia; S, visual-spatial agnosia. Under "Weigl's test" P signifies pass; F, fail.

Case	*Disability*	*Weigl's test*	*Similarities*	*Arithmetic*	*Block designs*	*Picture arrangement*
			LEFT FRONTAL			
1	O	F	2	2	−5	—
2	D	F	0	7	4	3 (0)
3	D	P	1	5	2	—
4	O	F	3	3	−1	0 (0)
5	O	F	4	—	0	1 (1)
6	D	P	1	1	1	—
7	O	P	3	—	0	−1 (0)
8	O	P	0	−3	2	5 (1)
9	O	P	1	8	2	3 (4)
10	D	P	0	1	−6	−1 (0)
11	D	F	4	5	3	4 (1)
	Means		1·7	3·2	0·2	1·8
			LEFT PARIETAL			
12	D	P	3	3	1	—
13	D	P	4	—	2	−1 (0)
14	D	F	0	7	−1	—
15	D	F	4	6	3	4 (0)
16	C	P	−1	3	4	—
17	O	P	−4	—	1	−1 (0)
18	C,D	P	3	6	5	—
19	O	P	3	—	0	−1 (0)
20	O	P	5	10	6	9 (1)
21	D	P	6	7	1	5 (1)
22	D	P	8	8	2	1 (1)
23	O	P	3	2	3	0 (0)
24	D	F	2	5	4	—
25	D	P	2	0	1	1 (0)
26	O	P	4	8	0	4 (0)
	Means		2·8	5·4	2·1	2·1
			LEFT TEMPORAL			
27	O	P	5	−3	−4	—
28	O	P	4	−2	1	−4 (0)
29	D	P	5	7	2	—
30	D	—	2	2	1	4 (0)
31	D		8	−3	−1	2 (0)
	Means		4·8	0·2	−0·2	0·7
			RIGHT FRONTAL			
32	O	—	−3	−9	−6	—
33	O	P	0	4	0	0 (1)
34	O	P	−1	6	0	—
35	O	P	−1	—	3	5 (0)
36	O	P	3	—	2	4 (2)
37	O	P	2	—	0	0 (0)
38	O	P	1	−3	0	0 (0)
39	O	P	3	—	4	7 (2)
40	O	P	2	0	3	4 (1)
41	O	P	2	4	−1	4 (1)
42	O	P	2	5	6	9 (5)
43	O	P	2	—	2	4 (6)
44	S	P	−1	0	4	5 (6)
45	O	P	2	8	4	2 (1)
46	O	P	2	4	4	4 (3)
47	O	P	2	5	4	5 (10)
	Means		1·1	2·2	1·8	3·8

TABLE III—(*contd.*)

			RIGHT PARIETAL			
48	S	P	−1	10	5	—
49	S	P	0	−2	7	—
50	S	P	2	−1	6	—
51	S	P	2	4	3	—
52	S	F	−6	0	2	4 (5)
53	S	P	−4	—	4	—
54	O	P	—	—	2	—
55	S	P	2	4	8	6 (0)
56	O	—	2	3	4	—
	Means			3·0	4·6	
			RIGHT TEMPORAL			
57	O	P	−1	3	−1	—
58	S	P	0	−1	6	7 (1)
	Means		−0·4			

Examination of these results show no significant relationship between laterality of lesion and impairment on the "non-verbal" abstraction test, although a significant relationship has been shown elsewhere with a larger series of patients (McFie and Piercy, 1952). Impairment on the "verbal" intelligence test is significantly greater with left-sided lesions, with the suggestion that this sensitivity is most marked with post-central lesions; and that this effect may be present in the absence of clinical dysphasia. Impairment on the arithmetical test is significantly greatest with left-sided parietal lesions. The visual-constructive test shows greater impairment with right-sided than with left-sided lesions, and in each hemisphere parietal lesions are associated with the greatest losses. The picture-arrangement test also shows more impairment with right than with left hemisphere lesions: there is also a suggestively greater loss with right than with left frontal lesions, a difference emphasized by evidence of a qualitative difference with lesions in these two situations, the former group tending more often to leave the pictures as presented.

IV. Discussion

The results are in agreement with the hypothesis that specific types of intellectual function are selectively impaired by lesions in different locations.[1] This is clearly illustrated by the evidence that the "verbal" test shows greater impairment with left- than with right-sided lesions, and greatest impairment with temporo-parietal lesions on the left side. This demonstration is consistent with our knowledge that language impairment is associated with dominant hemisphere lesions, and with Weisenburg and McBride's finding that intellectual impairment was greater with receptive than with expressive dysphasia. At the same time, our results indicate

[1]The results on subtests of the Bellevue scale show the same relation to laterality of lesion as was found by Anderson (1951), who used a different method of calculating the impairment.

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that this specific intellectual impairment may occur in the absence of clinical evidence of dysphasia: we conclude that impairment on this test represents damage to the intellectual antecedents of speech[1] rather than to the speech mechanism itself.

Similarly the "numerical" test shows a slight degree of impairment with lesions in all of the locations studied, but the impairment is greatest in cases of left parietal lesion. While this result stands in opposition to the findings of Weisenburg, Roe and McBride, it is in agreement with the general observation that acalculia is related to lesions in this area; and we may conclude that, as in the case of the verbal test and speech, the arithmetic test reveals impairment to the intellectual antecedents of calculation.

The results with the "visual-constructive" test show a more complex pattern, but one which nevertheless is consistent with earlier observations. The impairment, in either hemisphere, is greater with parietal than with frontal or temporal lesions, while it is also greater with right parietal than with left parietal lesions. Analysis of the causes of this impairment emphasizes this difference, as it is associated only in the right-sided cases with visual-spatial agnosia, while the patients with left-sided lesions have characteristically no impairment of visual space perception and in 2 cases there is evidence of frank constructional disability. This test, then, appears to be particularly sensitive to the higher levels of disturbance in space perception associated with right parietal lesions, and also, though to a lesser degree, to the constructional disability associated with left parietal lesions.

On the "picture arrangement" test, the evidence of greater impairment with right-sided lesions might be attributed to visual-spatial agnosia, and in the 2 cases with right parietal lesions their disorderly arrangement of the pictures supported this view; but the considerable impairment on this test in cases of right frontal lesions was not associated with any disturbance of spatial perception. The distinction between the performance of cases with right frontal lesions and those with lesions in other locations is emphasized by the evidence of a qualitative difference in their approaches to the task: the "right frontal" patient tended more often to leave pictures in the presented order. This tendency is reminiscent of Goldstein's (1948) concept of "stimulus boundness," one of the features ascribed by him to the change from the abstract to the concrete attitude. We may recall that Rylander noted a significant difficulty in arranging pictures in his patients with frontal ablations, but found no specific relation to side of lesion, while McCullough (1950) found this to be the most sensitive of all the Bellevue subtests to leukotomy. Clearly these results raise problems

[1]A phrase borrowed from Rylander, and implying intellectual activity confined to the framework of the function concerned.

which require a further elucidation; but, as they stand, they do not appear to contradict the general view that frontal lobe damage results in difficulty in synthesizing or relating stimuli in accordance with new concepts or experiences, and that among the reasons for earlier failures to demonstrate some change in performance (cf. Hebb, 1945) is probably failure to use appropriate tests.

The results with tests involving abstraction are, however, less in keeping with the results of earlier investigations. The Similarities test involves the process of abstraction, but it has already been referred to as a "verbal" intelligence test and its sensitivity to dominant hemisphere lesions is not therefore unexpected. Weigl's test, on the other hand, is a non-verbal abstraction test; and while the results of the present series are only suggestive, with a larger series of patients McFie and Piercy (1952) found significantly more frequent impairment on this test with left- than with right-sided lesions. The general conclusion is that, contrary to Goldstein's assertion that lesions of any location result in the impairment of "abstract attitude," the process of abstraction is in fact specifically impaired by dominant hemisphere lesions.

Parenthetically, a further distinction may be noted between functions selectively damaged by lesions of the dominant and non-dominant hemispheres. We may contrast the damage to abstraction (whether with verbal or visual material) associated with dominant lesions, with the damage to spatial and practical performances associated with lesions on the non-dominant side. Weisenburg, Roe and McBride also noted that, although composed of verbal material, their Analogies test was impaired by lesions of the right rather than the left hemisphere. Now these observations may be related to Spearman's theoretical claim, that "intelligence" consists of "the eduction of relations and of correlates"; for performances involving abstraction are cases of "eduction of relations", while analogical thinking and inferential reasoning[1] are cases of "eduction of correlates." Moreover, commenting on the mechanical or spatial "factor" revealed by psychological tests, Spearman and Wynne Jones observed (p. 136) that "in the first place, the factor is concrete, not abstract. In the second place, its form is of that kind designated as correlate eduction." It is interesting to observe, therefore, that intellectual functions most sensitive to dominant hemisphere lesions appear to be cases of "eduction of relations" while functions sensitive to minor hemisphere lesions may be classified as cases of "eduction of correlates."

So far, our results support the evidence of the existence of "factors" in intelligence, and indicate that, while a relatively slight localized lesion reveals itself, as in the majority of these cases, as intellectual loss, a more severe lesion, implicating the "mechanical" substrate of each factor results in the "verbal" loss becoming clinically apparent as aphasia; the "numerical" as acalculia; and the "spatial" as visual-spatial agnosia. The results suggest, in fact, that there may exist other "factors" corresponding

[1]The one function impaired in Lidz's (1939) case of right frontal lobectomy.

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to the abilities damaged in constructional apraxia and involved in the "picture arrangement" test.[1]

On retention tests, however, in spite of the uncertain estimates of the size of the lesions and the relatively crude methods of scoring the tests, the absence of relationship between extent of impairment and locus of lesion, together with the finding of considerably greater impairment with large lesions as a whole than with small lesions, stands clearly in support of the view that impairment of retentive function depends on the size of the cerebral lesion rather than its location—the essential conclusion which may be drawn from Lashley's experiments. The results indicate also that this evidence of general impairment appears to bear no consistent relationship to the presence of raised intracranial pressure; and they support Spearman's view that retention is a process qualitatively different from intellection.

Evidently then, the results of a suitable group of intellectual tests can be of value to the neurologist in the assessment of cases of cerebral lesions. Retention tests, as observed by Zangwill (1943), are of particular value in the estimation of general deterioration, while—although our results indicate that there may be some variability of effect—the results of tests of specific abilities may suggest the presence of a focal lesion. But here it must be noted that the demonstration of specific intellectual loss in association with a localized lesion depends on the fact that, in the individual normal subject, varied intellectual abilities reach much the same level, in comparison with the performance of the rest of the population. It is this aspect of intelligence which is "unitary," and, in this sense, factorial and unitary definitions of intelligence are both valid.

Summary

The results are presented of a study of 58 patients with localized cerebral lesions, examined with tests of abstraction, retention and learning and with subtests of the Bellevue scale of intelligence tests. These results tend to confirm the view that impairment of retention and learning is related to the size rather than to the locus of a cerebral lesion, while other intellectual abilities are selectively impaired by lesions in different locations. These abilities, corresponding to the "factors" concerned with verbal, numerical, and spatial thinking, are described as the intellectual antecedents of those processes which, in their ultimate dissolution, are known to the neurologist as aphasia, acalculia, constructional apraxia and visual-spatial agnosia and indicate lesions in specific locations. There appears to be a particular relationship between frontal lobe lesions and

[1]Perhaps the former is related to the F factor mentioned by Spearman and Wynne Jones, and the latter related to Thurstone's Reasoning factors.

TABLE OF TEST RESULTS

Bellevue subtests as equivalent scores.
Learning tests as numbers of repetitions needed.
Qualitative results as pass (P) or fail (F).

Case	*Age*	*Vocabulary*	*Picture completion*	*Similarities*	*Arithmetic*	*Blocks*	*Picture arrangement*	*Digit span*	*Digit symbol*	*Digit learning*	*Babcock sentence*	*Memory for designs*	*Weigl's sorting*	*Wechsler's deterioration*
1	36	10	10	8	8	14	—	7	—	3	8	P	F	4%
2	44	14	13	14	7	8	9	6	7	—	8+	F	F	32%
3	43	10	13	11	7	8	—	6	5	6+	10+	P	P	30%
4	35	11	13	9	9	12	11	9	7	5	9	P	F	20%
5	44	5	7	2	—	4	3	3	—	4	8+	—	F	30%
6	56	11	10	8	8	7	—	7	—	8	10	F	P	10%
7	51	14	14	10	—	12	12	7	7	2	4	P	P	20%
8	38	14	13	14	17	11	8	11	13	2	3	P	P	4%
9	20	8	10	8	1	7	6	4	3	2	—	F	P	40%
10	34	12	10	11	10	16	11	6	7	4	10	P	P	6%
11	16	11	12	8	7	9	8	9	6	6+	5	P	F	30%
12	23	11	7	6	6	8	—	6	4	3	6	—	P	33%
13	31	10	12	7	—	8	11	7	—	2	3	—	P	32%
14	43	8	—	8	1	7	—	4	—	4	12	—	F	40%
15	52	14	6	5	3	5	3	7	—	5+	8+	F	F	35%
16	46	10	9	10	6	4	—	6	—	9+	—	F	P	27%
17	47	14	9	15	—	9	11	13	9	2	2	P	P	3%
18	50	8	—	4	1	1	—	4	—	4	8+	F	P	46%
19	61	13	10	7	—	9	9	10	—	4	8+	F	P	0%
20	20	13	12	8	3	7	4	7	—	2	—	F	P	56%
21	21	13	14	8	7	13	9	6	6	2	—	P	P	40%
22	43	16	12	6	6	10	11	10	—	5	8	P	P	30%
23	29	9	13	8	9	8	11	6	5	3	4	P	P	36%
24	65	13	—	8	5	5	—	4	—	3	—	—	F	10%
25	56	9	13	7	9	7	7	4	—	4	—	F	P	20%
26	22	11	13	8	4	12	8	9	5	3	5	P	P	28%
27	51	11	—	5	13	13	—	7	7	3	12	P	P	0%
28	36	8	7	4	10	6	11	9	6	3	6	F	P	0%
29	35	13	10	7	5	9	—	7	—	2	8+	P	P	29%
30	42	14	10	10	10	9	6	11	—	4	8+	P	P	9%
31	26	12	15	6	17	15	12	10	12	—	3	P	—	0%
32	43	9	—	12	18	13	—	6	—	3	—	F	—	0%
33	31	12	14	13	9	12	12	13	9	—	7+	P	P	14%
34	44	13	11	13	7	10	—	10	—	4	3	F	P	15%
35	41	13	—	14	—	8	6	10	—	9	2	F	P	24%
36	43	11	12	9	—	8	6	10	5	2	5+	F	P	25%
37	41	14	11	11	—	11	11	9	9	3	6	P	P	14%
38	48	14	12	11	15	11	11	10	7	3	—	P	P	6%
39	37	10	13	9	—	7	4	7	—	8+	—	F	P	35%
40	58	17	13	11	13	9	8	11	4	5	—	P	P	20%
41	50	14	13	11	9	13	7	7	9	2	2	F	P	28%
42	30	13	14	12	9	7	4	10	4	2	2	F	P	40%
43	41	12	12	10	—	8	6	6	6	5	—	F	P	35%
44	58	13	9	10	9	4	3	7	—	4	—	F	P	21%
45	27	10	13	10	4	8	10	11	8	6+	—	P	P	30%
46	28	13	11	10	8	8	8	7	—	9	5	—	P	38%
47	51	13	13	10	7	7	5	11	6	4	5	P	P	5%
48	55	13	—	12	1	5	—	6	—	—	5	F	P	51%
49	55	14	11	11	13	3	—	—	—	—	3	F	P	41%
50	47	12	—	9	12	4	—	6	—	3	10+	F	P	27%
51	46	13	10	9	7	7	—	10	4	5	8+	F	P	30%
52	53	—	8	13	7	4	1	13	—	—	6	F	F	—
53	52	13	8	14	—	5	1	14	—	—	—	F	P	—
54	47	13	13	—	—	9	—	7	—	2	3	F	P	27%
55	47	14	13	11	9	4	6	9	4	4	3	F	P	39%
56	16	8	12	8	7	6	—	6	7	6	—	P	—	35%
57	24	12	14	14	10	14	—	13	—	2	3	P	P	5%
58	36	16	12	14	15	7	6	—	3	—	3	—	P	15%

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impairment on a test involving arrangement of pictures to tell a story. The loss of different features of Goldstein's supposedly unitary "abstract attitude" is found to be similarly related to the presence of lesions in specific areas.

At the same time, the demonstration of these differential effects of focal lesions depends upon the fact that the normal individual tends to reach the same level in all his abilities; and to this extent, intelligence shows a "unitary" nature.

We are indebted to Members of the Staff of the National Hospital for permission to make references to their cases and to results of special investigations made in their departments. We are also particularly grateful to Dr. Eliot Slater and Professor O. L. Zangwill for their assistance, advice and encouragement in this work.

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EFFECTS OF A RIGHT-SIDED OCCIPITO-PARIETAL BRAIN INJURY IN A LEFT-HANDED MAN

BY

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ATYPICAL cerebral syndromes associated with anomalies of handedness are of considerable theoretical interest. Hermann and Poetzl, in their book on agraphia (1926, pp. 1–31), reported in great detail a case in which this symptom was produced by a verified occipito-parietal lesion of the right hemisphere. Their patient is stated to have been ambidextrous. In addition to agraphia (which was the main presenting symptom), the patient showed moderate dysphasia and dyslexia, mild dyspraxia and a severe degree of finger-agnosia. The striking point, however, was that *symptoms conventionally ascribed to lesions of the minor hemisphere were also present*. Of these, the most evident was systematic neglect of the left half of the body and failure to make spontaneous use of the left limbs (autotopamnesia, Gerstmann, 1942). This deficit has hitherto been described only in connexion with lesions of the minor parietal lobe (Nielsen, 1938, 1946; Russell Brain, 1945; Critchley, 1951). In this case, then, as Nielsen (1938) has pointed out, symptoms normally associated with major and minor parietal lobe lesions respectively were produced by a lesion involving the right hemisphere alone.

A case somewhat similar to that of Hermann and Poetzl (1926) has more recently been described by Russell Brain (1941). This was a case of right parieto-occipital abscess, verified at operation (Russell Brain, 1941, Case 6). The patient is stated to have been left-handed as a child and he still used the left hand for cutting bread and dealing cards, though he wrote with his right hand. The principal symptoms were dysphasia, dysgraphia and dyslexia (with some tendency to read from right to left), severe ideational dyspraxia and some disorientation for left and right. In addition, however, there was *marked unilateral neglect of visual space* associated with a consistent preference for right-hand turns in route-finding. As Russell Brain points out, this form of disorientation is entirely characteristic of a lesion of the minor hemisphere. There was no evidence

of visual object-agnosia or topographical memory loss, suggesting that the shift of dominance for symbolic functions to the right hemisphere did not convert the latter into the major hemisphere for visual recognition and topographical skill. Russell Brain is therefore led to conclude that "... symbolic thought and expression, visual recognition of objects, visual orientation in space, topographical memory (Nielsen, 1940) and awareness of the body are functions which behave independently of each other in relation to cerebral dominance, and that in the case of any one of them the function normally performed by the left hemisphere may be transferred to the right without the occurrence of a similar shift in the others" (Russell Brain, 1941, p. 267).

In both the above cases, a right-sided occipito-parietal lesion in a left-handed (or partially left-handed) patient gave rise to symptoms characteristic of minor as well as major hemisphere involvement. The analysis of such syndromes is not without relevance to parietal lobe symptomatology and has also an important bearing on the wider questions of cerebral dominance. For these reasons, and also in view of their comparative rarity, it may prove of value to place a further example of a "mixed" occipito-parietal syndrome on record.

Case Report

The patient was an officer, aged 31, who had always regarded himself as *left-handed, though he wrote with his right hand.* He consistently used his left hand for fine manipulation (e.g. using tools) and for dealing cards, and he played all games left-handed. He preferred to kick with his left foot. There was no family history of left-handedness and two siblings were reported to be strongly right-handed. The patient had always had a mild hesitant stammer. His general intelligence was in the superior adult range and he had received a University education. In civil life he was a business man.

Case No. 8846.—On 29.6.44 this officer sustained a direct hit from a mortar bomb on the right side of the head, causing a wound about the size of a halfpenny in the right occipito-parietal region.

On *examination eighteen hours after injury* (Captain Watt), the patient was rational though dysphasic. He stated that he had had difficulty in understanding speech at first but that this had now improved; also, that he had known what he wanted to say but that his words were jumbled. Retrograde amnesia was assessed as "a fraction of seconds" and post-traumatic amnesia as "about one hour." The principal neurological findings at this time were left homonymous hemianopia, extending almost to fixation point, profound sensory disturbances on the left side of body, left-sided motor disability (probably in part dyspraxic), and a well-marked nominal dysphasia with some tendency to perseveration. The left deep reflexes were brisker than the right. Right plantar flexor; left absent. There were numerous paraphasic errors in spontaneous speech, slight dyslexia and pronounced dyscalculia.

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The patient was somewhat euphoric and facetious, though not without some insight into his disabilities.

At *operation* (Major Small), thirty hours after injury, the scalp was excised and bone removed all round to expose normal dura. Much lacerated brain and blood clot herniating through large dural tear and laceration were removed with suction. Intracerebral portion of lacerated brain and two bone fragments removed from track with sucker and a cyst of C.S.F. found which, when opened, led down into the ventricle where a bone fragment was found lying laterally within the lateral wall of the temporal horn just as it makes its exit from the trigone. 5,000 units sodium penicillin inserted into ventricle; dura left open and incision closed with drainage.

On admission to a *Military Hospital* (*Head Injuries*) on 1.7.44 the patient was well orientated and gave a clear account of his movements subsequent to injury. On *neurological examination* his spontaneous speech was moderately dysphasic, with some hesitation and obvious circumlocation. He occasionally uttered an incorrect (though not wholly unrecognizable) word. He named 17 out of 20 common objects correctly and, in case of failure, would always accept the correct name and reject others. In reading aloud, there were many omissions and obvious difficulty in following the lines. There was occasionally failure to comply with requests, probably due to mildly defective comprehension. No dyspraxia in using objects or performing pantomime actions with the right hand. Visual acuity J1 in both eyes. Visual fields to confrontation showed left inferior quadrantic defect extending to fixation point. Fundi and pupils normal. Other cranial nerves intact. Left hemiparesis with decreased reflexes and tone. Abdominals absent; left plantar extensor. The left arm could be adducted and internally rotated at shoulder, with extension of elbow and flexion of fingers with hyperpronation. No other movements possible. Movement of the left leg about 25 per cent of normal. Sensory changes on left side very gross: Diminution to pin-prick over whole left side of body; loss of two-point discrimination, joint position sense and tactual localization on left, maximal in left arm and hand. General condition at this time very satisfactory.

Skull X-rays (8.7.44) showed large operative defect in upper part of the right parietal bone, from which fissuring extended coronally in both directions. No evidence of indriven bone-fragments seen.

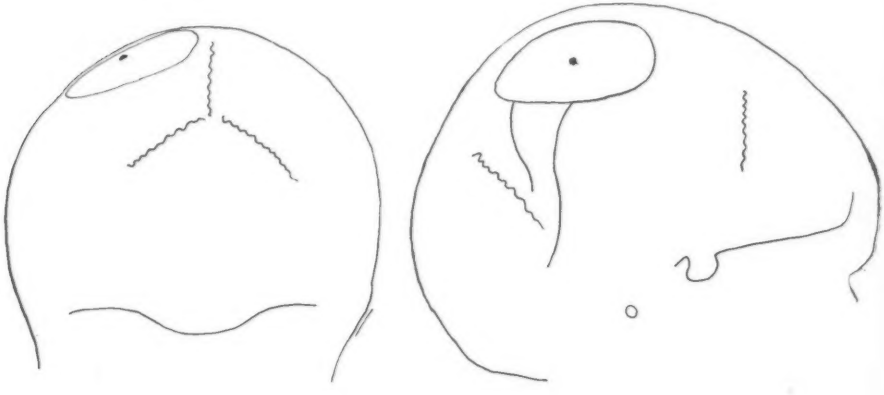

FIG. 1.—Tracings from radiographs.

Progress.—Three days after admission power showed marked improvement; elbow flexion was not present and it was suspected that much of the motor disability arose on a sensory basis. *One week* after admission the field defect was restricted to one of disorientation and inattention in the left lower quadrants. Total loss of position sense, including hip and shoulder joints, was still present. *Speech* was still hesitant and *writing* showed striking defects of grammar and some tendency to omit, reduplicate or transpose articles, prepositions, etc. Alignment of the lines on the paper was poor, with some tendency to deviate upwards and to the right. ***Spelling was unaffected.*** Two extracts from letters written at this time may be given:

7.7.44: "I am afraid I will be long time before I am better. As you may gather have got fractured skull and I of my arm are not much good. I will be O.K. in by about 6 weeks ? time. The hope will be O.K. for the moment about writing is pretty difficult and as soon as I have some sense writing write again."

11.7.44: "Many thanks for your letter. Am afraid he it will be very long time for O.K. again. I have fractured skull and left arm is partly paralysed and cannot read properly yet. . . . I speech is getting on pretty stupid still."

One month after admission the patient was still given to periphrasis and circumlocation in his speech but his letters were normal in construction, expression and spelling. He was able to give quite a good account of a book he had recently read but missed one or two key points in the story. He could now walk unaided, though slowly and there was still slight weakness of the left hand and foot, probably due to the gross cortical sensory loss. He could, however, now name correctly movements of considerable range at ankle-joint though not at all in the toes. There was still gross loss of position sense in the left fingers and at wrist though he perceived and named movements of the elbow correctly. He complained of some difficulty in concentrating and collecting his thoughts, and in memory.

Six weeks after admission there was still evidence of partial left quadrantic homonymous field defect. The cortical sensory impairment was pronounced though a little less severe than previously. Reading aloud was mildly defective and the patient failed to retain correctly what he read on short tests. There was also evidence of *loss of spatial orientation* at this stage. When out in the street, the patient reported that he was liable to feel suddenly lost and his surroundings appeared unfamiliar. He might then lose his way completely. *Plan-drawing* at this stage was very poor (cf. fig. 2). On 23.8.44, Brig. Cairns reported: "Has been going down to town and is apt to charge into middle of road or off at an angle when crossing at traffic lights. Knows his direction and the situation of his objective all right but mixes right and left." He also noted that the patient tended to confuse left and right on ordinary clinical tests.

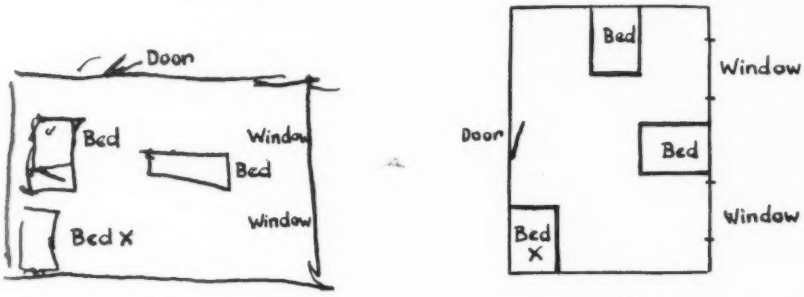

FIG. 2.—Ground-plan of room: A, Drawing by patient. B, Drawing by examiner. X = Patient's bed.

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The patient made good progress and was transferred to a rehabilitation centre on 25.8.44. On his return one month later, Brig. Cairns noted some improvement in facility of left hand, and in speech, but he still confused left and right and was slow in dressing. He had visited London (where he normally lived) and found his way about fairly well, though had made some mistakes.

On *neurological re-examination,* visual fields were full to confrontation, apart from questionable disorientation in left half-fields. Other cranial nerves intact. Motor power 90 per cent normal. All tendon reflexes slightly brisker on left; left plantar extensor. Impairment of exteroceptive sensation still present over whole of left side, including face. Vibration sense markedly impaired. There was practically 100 per cent position sense defect in proximal joints and 100 per cent defect in fingers and toes. Loss of two-point discrimination over whole of left hand and foot (even with 8 in. separation). No nominal speech defect in evidence but comprehension still a little impaired. On 11.10.44, the patient was discharged home on leave for a period of three weeks.

On 13.11.44, *four months after injury,* a tantalum graft was inserted (Brig. Cairns), from which operation the patient made a good recovery. On *examination prior to discharge* (6.1.45) the principal residual disabilities were defective position sense in left limbs, impaired localization and two-point discrimination in left hand and foot, slight diminution of exteroceptive sensation on left side, very slight generalized weakness on left, with increased reflexes, and residual dysphasia and kindred psychological deficits.

Visual fields.—On 19.7.44 perimetric charting showed a partial left lower quadrantic defect, extending to 8° from fixation point. In the defective area, a stationary test object appeared "shadowy" and readily disappeared from vision when moved. On 16.8.44 fields were full apart from some blurring of 2/2,000 and 5/2,000 test objects in the left lower quadrants. On 10.11.44 this blurring was less pronounced but the patient stated that test objects appeared "weaker" in the peripheral parts of the left inferior quadrants. A final charting on 28.5.45 (fig. 3) showed full fields apart from a minute scotoma in the right eye.

EEG examinations (W/Cdr. Denis Williams).—On 22.8.44 the EEG showed a gross focal abnormality in the right posterior parietal and posterior temporal regions consisting of medium voltage 1–4 a second waves. The records from the left hemisphere were within normal limits and showed a stable dominant frequency of 9½ per sec. No specifically epileptic activity was seen at rest or after overbreathing. On 20.12.44, the EEG record showed a marked improvement, but there were still medium voltage slow waves throughout the right hemisphere, particularly anteriorly. There was a diminution in voltage of all frequencies in the right parietal region, which was thought to be partly due to the tantalum plate.

Psychiatric examinations (Major W. R. Reynell).—On 17.8.44 (seven weeks after injury), psychometric tests showed intellectual loss in both verbal and visual-constructive fields. The patient was unable to do any of the Kohs Block designs and failed on maze-tests appropriate to a mental age of 7 years. His score on Progressive Matrices was 35/60, the patient stating that he had scored 57 on this test one year previously. On 27.9.44 he still showed an almost complete incapacity on Block-Design tests but score on Progressive Matrices had risen to 44. He failed on the "block-counting" subtest at the X year age-level of the Stanford-Binet Scale, Form M. There was great difficulty in understanding simple logical problems of the type: "If A is greater than B, and B is greater than C, is C less than A?" Although formerly good at figures, the patient was now unable to subtract 2s. 0½d. from £1 in his head, and stated that he "now has to ask a taximan to take his fare from a collection of coins." There were also defects on tests presumed to involve

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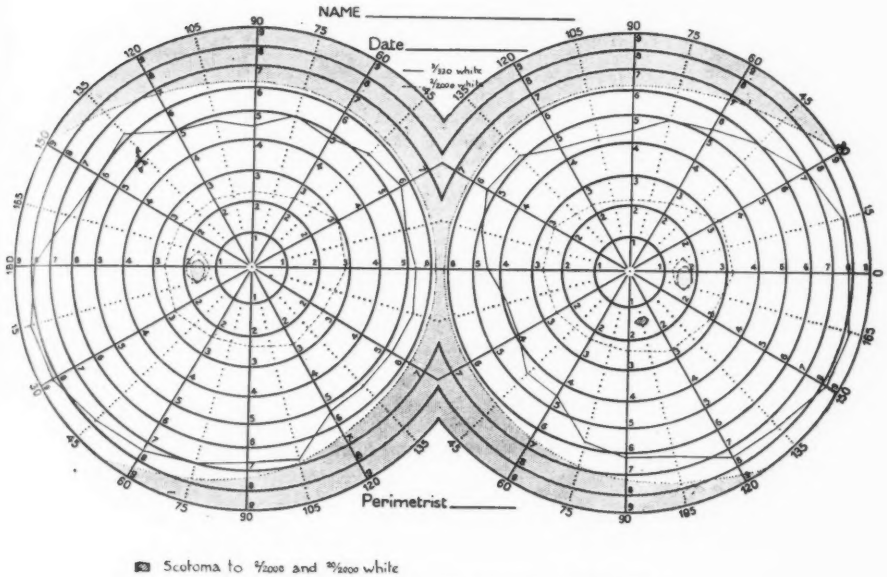

FIG. 3.—Visual fields eleven months after injury.

visual imagery (e.g. "divided cube" and "contained boxes"). *Summary:* "This officer . . . has improved somewhat but still shows impairment of spatial sense, verbal memory, calculation, and has a slight residual dysphasia both receptive and expressive."

On re-testing on 22.12.44 (six months after injury) the patient showed some further improvement. He could now solve 4 of the 7 Block-Design tests in standard time and Progressive Matrices score had risen to 47. But he was still unable to perform correctly on the Stanford-Binet "block-counting" subtest. On the *N.I.I.P. Group Test* 33 total score was 89/193, but rose to 144 with extra time allotted. The patient was notably poor on the subtests of analogies, mixed sentences and reasoning in this battery. Mental arithmetic remained much impaired. *Summary*: "Tests show intellectual loss in an officer of good pretraumatic intelligence. There is retardation on all tests. Only slight residual dysphasia but impairment of abstract thought, visual imagery, reasoning capacity, spatial perception, calculation and judgment. Attention is sustained with some difficulty and he is somewhat mistake-prone. His mood is mildly euphoric and there is some exaggeration of previous personality traits."

Follow-up inquiries.—On routine inquiry (by correspondence) *nine months* after discharge the patient complained only of numbness and weakness of the left side. After demobilization, he had returned to work with his old firm and had managed to cope with the work fairly adequately. But he experienced much difficulty with figures. A second inquiry *two years* after discharge yielded substantially the same information.

Condition four and a half years after injury.—The patient was readmitted for check-up on 10.6.49. At this time he reported three attacks of "stiffness and jumping" in the left leg which then spread to the left arm. He was advised to resume anti-

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convulsant medication. On *neurological examination* the principal findings were slight cortical sensory loss in left hand and foot, attention defect to touch in left hand and in left half-field of vision. The patient reported some residual difficulty in following complex directions and of slowness in reading. He also thought that his *visual memory* had changed in a somewhat indefinable manner: Scenes familiar to him from before his injury had apparently lost their old associations and were apt to appear to him as lacking in sense of familiarity. There was also slight defect of short-term recent memory and episodic absent-mindedness.

A further follow-up inquiry (15.11.49) yielded the information that the patient had started to *dream* again, for the first time since his injury (cf. Humphrey and Zangwill, 1951, Case 3). He reported two focal epileptic attacks in the left lower limb, without loss of consciousness. In general he had maintained his progress and remained active in his professional life.

Psychological examination six and a half years after injury.—On 21.12.50 the patient kindly consented to attend for interview by the present writers regarding his residual psychological handicaps. The principal findings are as follows:

(1) *Dysphasia:* The patient reported no residual speech defect (apart from the pretraumatic mild stammer) but some slowness in reading and writing. He was slow in picking up the full sense of what he read, especially when the material was abstract, and seldom read a novel. His written composition was quite normal and he could also dictate to a secretary. On oral reading tests the patient was a little slow and there was a minimal tendency to paralexic word-substitution (e.g. "night" for "might"). No spelling defect on oral or written tests.

(2) *Dyscalculia:* There was rather marked residual defect in both mental and written arithmetic. He still makes mistakes with change. Performance on Wechsler Arithmetic subtest was impaired.

(3) *Drawing and copying:* A bicycle was drawn in a sketchy manner, with obvious disconnexion of parts (fig. 4). In drawing a daisy (Critchley, 1951) the

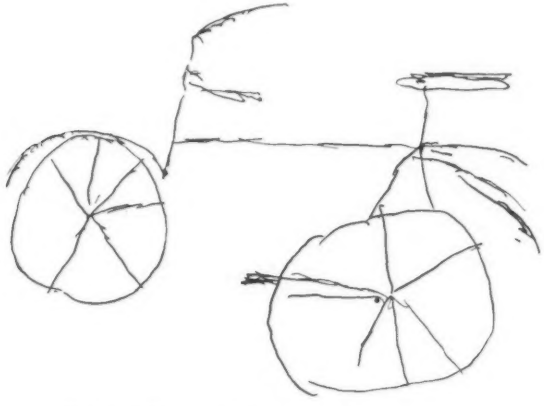

FIG. 4.—Drawing of bicycle from memory.

patient drew the petals on his right-hand side first and then rotated the paper so as to bring the left-hand half of the paper on to his right-hand side. A map of England was drawn adequately, apart from omission of the left-hand side and

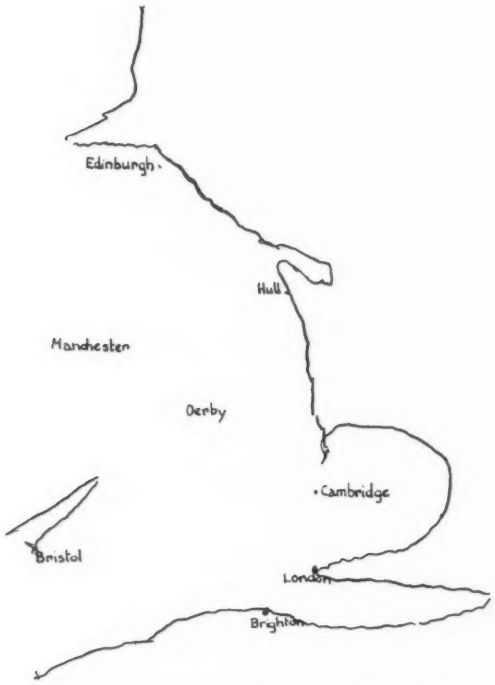

FIG. 5.—Map of England drawn from memory.

coast-line (fig. 5). He was able to copy the Stanford-Binet "Key" pattern correctly but, in reproducing it from memory, had great difficulty in drawing the left-hand side of the diagram, which was left till the last.

(4) *Spatial judgment:* The patient passed the first part but failed on the second part of the Stanford-Binet *Paper-cutting* subtest (Form L, IX, 1). He failed on 4 of the 14 items on the Stanford-Binet *Block-Counting* subtest (Form M, X, 1). These findings indicate fairly marked residual visual-spatial loss.

(5) *Unilateral agnosic disabilities:* A tendency to neglect the left half of visual space (despite full recovery of the field defect) is evident from the above test findings. The patient had insight into this disability and noticed that he still tended to bump into objects on the left side. But he had noticed no consistent tendency to neglect doors or turnings on his left. The patient also remarked that he had tended to neglect the left side of his body completely for about six months after injury. Although it will be borne in mind that the left-sided sensory loss was very gross in the earlier stages, it is possible that there was at this time an additional agnosic neglect of the left side and loss of spontaneity in the use of the left limbs.

(6) *Right-left orientation:* No residual difficulty in discrimination of right and left could be detected, although the patient confirmed that this had been severe at first. No finger-agnosia now (or previously). No residual dressing disability though the patient confessed that he used to get into "a most appalling tangle" with his clothes in the first six months after injury.

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(7) *Spatial orientation:* The patient reported that he was still liable to become momentarily confused as to his sense of direction, especially when flustered, but that his orientation was "not too bad" when he was able to take his time. In the early stages, he said, he had often found himself "completely disorientated," even in places formerly well known to him. He had occasionally misidentified familiar buildings. Railway stations gave him considerable difficulty and he once boarded a train going in the opposite direction to his destination. Very occasionally he had had momentary lapses in which he could not remember exactly what he was doing in a given place—what precisely his "aim and object" were at the time. These topographical troubles had receded almost completely in the last year or two. The patient could describe routes and landmarks in London with reasonable accuracy and his topographical memory (on rough testing at least) did not appear to be impaired.

(8) *Visualization:* The patient stated that his visualization had much improved and that he now had no difficulty in recognizing either people or places. He confirmed that he had begun to dream again about a year previously.

(9) *Handedness:* It was stated by the patient that he now used his *right hand* for most purposes, whereas formerly he had been left-handed for everything except writing. He now only dealt cards with his left hand. On a variety of manipulative tests, the patient showed a consistent preference for the right hand.

(10) *Intelligence:* Rough testing suggested little or no general post-traumatic intellectual loss. There was some evidence of difficulty in sustained concentration and occasional absent-mindedness.

Summary.—This left-handed officer presented a complex syndrome following a right-sided occipito-parietal G.S.W. On early examination the principal findings were left homonymous hemianopia, profound left-sided cortical sensory loss, left-sided motor disability (probably in part dyspraxic and in part due to sensory defects), and mixed dysphasia. These symptoms underwent considerable improvement and, two months after injury, fields were full apart from mild attention defect and disorientation in the left inferior quadrants and the dysphasia was much improved. There was, however, gross neglect of the left half of visual space (and, more questionably, of the left half of the body), dressing dyspraxia, confusion of right and left, pronounced visual-constructive loss, and some disturbance of spatial orientation. No visual object-agnosia or finger-agnosia was elicited at any stage. Writing showed early disturbances of a paragrammatic character but there were no defects of letter-formation or spelling. On psychological tests there was moderate impairment in both the verbal and non-verbal spheres. Calculation was grossly impaired and the defect outlasted the disturbance of spoken language. On discharge residual disabilities were moderate left-sided sensory loss, slight generalized weakness on left and moderate intellectual loss.

Six and a half years after injury residual defects in the psychological sphere were very slight dyslexia, moderate dyscalculia, fairly marked unilateral spatial agnosia and visual-constructive loss, mild topographical disabilities and slight generalized weakness of concentration and memory. Hand-preference had shifted to the right hand for practically all everyday purposes.

Discussion

The general picture in this admittedly complex case corresponds fairly closely to the cases of right-sided occipito-parietal lesions with anomalous handedness described by Hermann and Poetzl (1926) and Russell Brain (1941). As conventional indications of *major* hemisphere involvement,

one may list the presence of dysphasia, dyslexia and dysgraphia (though without impairment of spelling), pronounced dyscalculia, early dyspraxia, right-left disorientation and impairment on verbal intelligence tests. As indications of *minor* hemisphere involvement, the least disputable is undoubtedly the massive neglect of the left half of visual space (unilateral spatial agnosia), which persisted after full recovery of the visual field defect and was still in evidence over six years after injury. As we have said, there may well have been a parallel tendency to neglect the left half of the body (autotopamnesia), though in view of the gross left-sided sensory loss, the unilateral spatial agnosia and the lack of early inquiry specifically directed to this point, the existence of an additional body-scheme defect cannot be taken as established. It will be remembered that this feature was very striking in Hermann and Poetzl's patient whereas left-sided visual neglect was clearly in evidence in the case described by Russell Brain.

In addition to the left-sided agnosic symptoms, the patient presented in marked degree two further features which, although not unknown with lesions of the major hemisphere, occur with surprising frequency in cases of minor parietal lobe involvement. These are first, dressing dyspraxia, which according to Hécaen and Ajuriaguerra (1942–5, 1951), is especially common and well marked in cases of right-sided posterior cerebral lesion: and secondly, visual-constructive defects of the type described in several recent studies of right-sided occipito-parietal lesions in right-handed individuals (Lenz, 1944; Paterson and Zangwill, 1944; Roth, 1949; McFie, Piercy and Zangwill, 1950; Hécaen, Ajuriaguerra and Massonet, 1951). Even if the correlation of these two features with minor hemisphere lesions is disputed, the presence of unilateral spatial agnosia alone in this case (as in that of Russell Brain, 1941) is convincing evidence of minor parietal involvement. It may be said, therefore, that *the patient presented "dual" (i.e. major and minor) parietal lobe symptomatology following a lesion of the right hemisphere alone.*

A comparison of the findings in this case with those in cases of the same type which have been previously reported reveals certain interesting points of difference. Unlike Hermann and Poetzl's patient, our subject presented no finger-agnosia, and, unlike Russell Brain's, no ideational dyspraxia. More important, however, are the differences between the three cases with regard to the disturbance of *writing*. In Hermann and Poetzl's case, there was initial and severe agraphia which was regarded as the main presenting symptom. It was expressed in grossly defective letter-formation, spelling and syntax. In Russell Brain's case, the patient is said to have been able to sign his name but to have shown paragraphia in writing a short sentence to dictation. In our case, on the other hand, the writing disorder was transient and was almost exclusively restricted to

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grammar. No defects of spelling or letter formation were in evidence at any stage. It is tempting to argue that the early paragrammatism in writing was secondary to the syntactical disturbance of spoken language and does not warrant treatment as a primary agraphia.

It is probable that the absence of any real agraphia in the present case is related to the patient's long-standing right-handedness for writing. It may be surmised that his preference for the right hand (whether inborn or a function of training) in writing indicates that the central mechanisms subserving this function had been organized in the left hemisphere. In Hermann and Poetzl's case, on the other hand, the severe agraphia obviously indicates a transfer of dominance with regard to writing (along with speech) to the right hemisphere. Although their patient's preferred writing hand (if any) is not stated, the findings create at least a *prima facie* supposition that it was the left. At all events, the data in our present case strongly indicate that writing may be subserved in an ambidextrous man by the hemisphere non-dominant for speech, thus providing a further illustration of Russell Brain's principle of dissociation of functions with regard to cerebral dominance.[1]

The defects of *topographical sense* shown by our patient are less easy to assess from the standpoint of dominance. In the earlier stages, at least, there can be little doubt that the constant neglect of the left half of the visual environment gave rise to an embarrassment in route finding precisely of the type described by Russell Brain (1941). In this respect, he displayed the form of spatial disorientation characteristic of a minor hemisphere lesion. On the other hand, certain of the topographical troubles were of a kind more commonly ascribed to lesions of the major hemisphere. Thus confusion of right and left (without clear-cut preference for right-hand turnings) was adduced by Sir Hugh Cairns as an important factor in his early episodes of disorientation. Further, the patient himself thought that some, at least, of his early difficulty in this sphere arose from episodic misidentification of buildings. Although such defects of recognition have been described in certain cases of right-sided injury in right-handed patients (Paterson and Zangwill, 1945), they are undoubtedly more common in connexion with lesions of the major hemisphere (Poetzl, 1928; Nielsen, 1940, 1946). Lastly, there was some evidence of a more general failure of conceptual grasp of topographical relationships of the kind so well described by Head (1926) in his cases of semantic aphasia. Indeed the patient showed many of the defects attributed by Head to this variety of language disorder. This, again, is evidence of a lesion involving the

[1]On the other hand, Dr. Russell Brain has pointed out to us that it is perhaps improper to speak of writing as being subject to cerebral dominance at all in a case of this kind.

major hemisphere. (On the other hand, topographical memory—in so far as could be ascertained on inquiry six years after injury—had at no time been affected.) It would appear, then, that in addition to the type of disorientation typical of a minor parietal lobe lesion, the patient presented certain features of topographical loss more consistent with a lesion of the major hemisphere.

It is important to point out that the picture in this case, despite its "dual" character, differs in a fundamental way from the typical syndromes of *bilateral* injury. In such cases, visual disorientation (Holmes, 1918, 1919), gross topographical loss (Kleist, 1934; Faust, 1947) and severe visual agnosic disturbances (Adler, 1944, 1950) are commonly found. The picture in the present case, despite the combined presence of both "major" and "minor" parietal signs, is clearly not equivalent to one of bilateral parietal injury. Thus the effects of a right parietal lesion in a left-handed man, despite the apparent concentration of function in the right hemisphere, are clearly far less grave than if both parietal cortices had been involved. This leads one to suppose that, in addition to the principle of unilateral representation and cerebral dominance, there is a *biparietal integrative function,* disturbances of which lead to symptoms very much more severe and long-lasting than those produced by lesions of the major hemisphere alone, on whichever side it may be.

An interesting feature of the present case is the *extent of restitution* of higher functions which took place after injury. Recovery of speech functions was surprisingly rapid and complete and there was considerable improvement in visual thought processes and spatial orientation. On examination six and a half years after injury, indeed, the patient presented but a trace of dysphasia and dyslexia and his general intelligence was little (if at all) depressed. Although precise comparison is difficult, it would appear that the extent of functional restitution was considerably greater than in the somewhat similar cases of semantic aphasia with spatial disorientation reported by Head (1926). With one exception (a strongly left-handed man), the lesion was left-sided in all Head's cases. It is hard to avoid supposing that the unusual degree of restitution in the present case was an expression of incomplete cerebral dominance. It will be remembered that the patient's manual preference shifted to the right hand after injury, despite only moderate residual impairment of the left. One may suggest, therefore, that right cerebral dominance in this case had never been established as completely as is the rule in the case of the left hemisphere in right-handed individuals (cf. Conrad, 1949). If this were so, it may be supposed that, after injury, the latent potentiality of the left hemisphere came spontaneously into play and made possible the very considerable restitution of higher cerebral function.

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SUMMARY

(1) A case of right occipito-parietal penetrating brain injury in a left-handed man is reported. It is pointed out that the lesion gave rise to symptoms ordinarily associated with lesions of the major and minor parietal lobes respectively. Two similar cases have previously been described in the literature.

(2) The absence of primary agraphia in this case (unlike those previously reported) is ascribed to the patient's preference for the right hand in writing. It is suggested that, whereas speech functions were represented in the right hemisphere, the central mechanisms governing writing had been organized on the left side.

(3) Some implications of the findings for the theory of cerebral dominance are briefly considered.

We wish to thank Professor Sir Hugh Cairns and Dr. W. Ritchie Russell for their encouragement and for their kind permission to publish this case. We have also to thank Sir Russell Brain for his stimulating and helpful comments on this paper.

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THE ORIGIN OF SENSATIONS OF HEAT AND COLD

BY

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WHEN an object at a higher temperature comes into contact with the skin a sensation of warmth is experienced; when the object is at a lower temperature the sensation is cold. Although these sensations are different in kind they are commonly regarded as being merely different in degree: i.e. as representing opposing aspects of a single physical cause, which is measured by the thermometer. Weber suggested that the sensations are produced by the process of change in temperature. This implies that when the temperature of the skin is no longer changing there are no such sensations. But it is common observation that when the skin is brought to a low temperature a persistent sensation of cold is experienced long beyond the period which could reasonably be regarded as required for equilibration, and it is similarly known that a persistent high skin temperature is associated with a continued sensation of warmth. A related difficulty in accepting Weber's theory arises from an experiment described by him: if the skin is vigorously cooled by the application of a cold object, the sensation of cold persists after the cold object is removed, although the area from which the sensation arose is now returning to its original temperature and should therefore give rise to a sensation of warmth. This contradiction of his theory Weber explained by physical arguments.

Hering (1877), influenced by his theory of colour vision, suggested another origin for these sensations. The skin acts like a thermometer responding to increase above a standard as warmth and to decrease as cold, but it differs from a thermometer in that as the temperature rises or falls, the standard or "zero" changes with it and quickly overtakes the change except only at extremes, when this process of adaptation, as he called it, is no longer adequate to neutralize the divergence of temperature. This accounts for the essential phenomena, but neither Hering nor any subsequent investigator has demonstrated or suggested an explanation of the process of adaptation, or produced independent evidence of its existence. Hering himself directed attention to the fact that this adaptatory process, if it exists, must have a double influence, for the shifting

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of the zero during a sensation of warmth entails also a shifting of the zero for cold with an opposite significance. He argued from this that it was improbable that the end-organs for warmth and for cold are separate structures, as a precise correspondence between two distinct processes in independent structures, only one of which was put into activity, is difficult to accept. As it has been since established that the end-organs for warmth and for cold are distinct, this argument can now be used in reverse and Hering's theory becomes by that the more dubious.

Other theories of the origin of these sensations have been proposed in which change in spatial gradients have been suggested as causal, particularly by Ebbecke (1917). It has, however, been shown by Hensel and Zotterman (1951) that cold impulses can be detected in the sensory nerve fibres coming from the isolated tongue kept at a steady low temperature. In such a preparation gradients of either type could not be present.

One criticism could be made, until recently, of the classical investigations. Very little was known, although much was surmised, about the actual temperature changes in the skin when a stimulating object was applied to it. Hensel (1950*a*) has devised an efficient method with which he has examined the actual changes. He has shown, among other things, that the alterations in temperature at a given depth and time are proportional to the difference between the initial skin temperature and the temperature of an object which causes it to alter, and that the rates of change in temperature have a similar relation. In another communication in which he gives a full account of the literature, Hensel (1950*b*) has shown that the physical changes which have been speculatively suggested to reconcile the Weber experiment with Weber's theory are not sustainable; and that sensations of warmth, not necessarily steady, may persist long after a thermocouple has ceased to indicate change in temperature. These results, as well as the experiment of Hensel and Zotterman which has been mentioned previously, present in established form the objections to the Weber theory. The objection to the Hering theory is that it is an unsustained speculation not easy to reconcile with the segregation of the origins of the two sensations.

If attention were limited to experiments in which the skin temperature did not vary widely from the normal the Weber theory would be satisfactory. But if attention were limited to extreme temperatures the Weber theory would fail but the facts could be adequately described in terms of the Hering theory for cold at low temperatures and for warmth at high and that too without invoking adaptation. Thus the reaction of the skin appears to be different at different temperatures. A systematic investigation of the reaction of the skin to thermal stimuli over the whole feasible range might be expected to yield clarification, since a theory

which for explanatory purposes divides the narrow range of tolerable skin temperature into three portions can scarcely be accepted without compelling evidence.

When the skin is brought to a temperature of 20° C. it is not possible either by brief heating or cooling to produce a sensation of warmth or of cold, although there is evidence that at still lower temperatures the power of response recurs to some extent (O'Connor, 1932). Hahn (1927) investigated the amount of change in surface temperature, at various initial temperatures, which is necessary to produce a threshold stimulus for warmth. He found that when the skin was below 33·5° the necessary temperature difference was such that when added to the initial temperature it resulted in a temperature of 33·5°. He used this conclusion as an argument for the Hering theory, but found himself forced to explain a threshold sensation above this point as being produced by a small rise in temperature. Hahn states, without giving detail, that cold sensations arise in a similar manner. Cold sensations were examined systematically by O'Connor (1935) using as the criterion of excitation, not the threshold sensation, but the sensation produced by a standard stimulus applied to an area of skin maintained at a standard temperature. The strength of the stimulus necessary to produce the same intensity of sensation at another area when kept at a different initial temperature was determined systematically for a wide range of initial temperatures. Then results were expressed as the reciprocal of these "equivalent stimuli," i.e. the excitability. The relation of the equivalent stimulus to the initial temperature was found to be complex. The necessity which Hahn found for distinct theories to explain the same phenomenon above and below 33·5° can scarcely be regarded as satisfactory. His conclusion about cold sensation is not in complete agreement with O'Connor's results. O'Connor's experiments, on the other hand, suffer from two defects: (1) the statistical calculation of the equivalent stimulus is not formally satisfactory; and (2) there was a technical fault in the method which might significantly vitiate the result. The skin was kept at the standard temperature by a temperator which consisted of a flat copper ring-shaped vessel surrounding a central tube through both of which a current of water at a fixed temperature flowed. In order to test the reaction the central tube was withdrawn and replaced by another similar tube containing water at a different temperature. The initial skin temperature was recorded by a thermocouple under the ring. As some time, though brief, elapsed between the withdrawal of the central portion of the temperator and the introduction of the test the skin actually tested must have changed slightly from the temperature recorded by the thermocouple. Although at low temperature the error would be small it seems likely that at high temperatures because

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of accompanying large blood flow there might be substantial error. Because of these uncertainties it was decided to reinvestigate the manner in which "the equivalent stimulus" was affected by the initial temperature for both heat and cold sensations by a method which avoided the technical faults and to analyse the results by a standard statistical method. The authors were alternately subject and recorder in successive series.

Sensations of Warmth

Method.—One forearm was immersed in a water bath the temperature of which was maintained at 33°–34°. The temperature of the surface of the skin at a point near the area to be tested was recorded by a thermocouple attached by a strip of adhesive plaster. A period of ten minutes was allowed for equilibration. A standard sensation of warmth was produced by applying to the selected area a flat-bottomed copper tube 1·5 cm. in diameter containing water at 40°. It was applied for 3 seconds, which is sufficient for the sensation to reach its maximum. This temperature difference of approximately 6½° was the standard test which was used throughout the series. The other arm was immersed in a second bath, the temperature of which was kept constant at another temperature. The temperature of this skin was also taken by a thermocouple. The area of it corresponding to that used for the standard test on the first arm was tested in a similar manner by tubes containing water at different temperatures which were varied so that the elicited sensation appeared sometimes more warm and sometimes less warm than that produced by the standard test which was applied for comparison alternately immediately before or immediately afterwards. The various observations were repeated until the recorder was satisfied that the range and number of them was sufficient. This number was of the order of seventy.

Examination of these data by Probit analysis (Finney, 1947) using the graphic method, gave the intensity of the stimulus, i.e. the temperature difference, which was equivalent to the standard stimulus. In a series of such experiments the whole feasible range of skin temperatures was examined in repeated experiments. An underlying assumption is that on every occasion the standard test results in a sensation of the same intensity. This is in fact not so. During the progress of an experiment the sensation resulting from the standard stimulus sometimes becomes perceptibly weaker. That this was due to "fatigue" was supported by the fact that after a period of rest recovery occurred. Occasionally, also, the standard test produced from the beginning an intensity of sensation differing from expectation. It seems likely, however, that these divergences are of central origin and affect both sets of observations equally. In most experiments it occasionally happened that it was not possible to decide

which of two compared sensations was the stronger. This was sometimes due to a momentary lack of attention and sometimes to a difficulty of deciding between the two sensations which becomes an impossibility as the recollection of both sensations fades. These failures, amounting to about 1½ per cent of all observations, were omitted in subsequent calculations.

Two sets of observations were made. In one of these the subject was O'Connor, the areas were over the middle of the back of the head of the radius. The average standard skin temperature was 33·3° (32·7 to 35·5), the standard test was 40°. In the second the subject was McCarthy; the areas

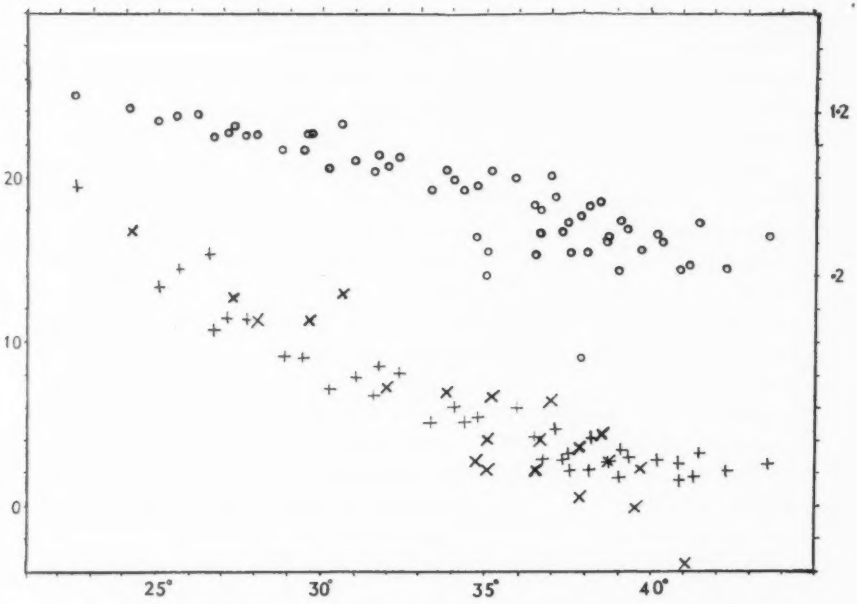

FIG. 1.—The relation between the initial skin temperature and the stimulus required to produce a standard sensation of warmth. Abscissæ: the initial skin temperature × observations on the first subject + observations on the second; ordinates, on the left, the strength of the stimulus in degrees centigrade. The circles indicate the logarithms of the stimulus strength, the ordinates are on the right.

were the dorsal surface of the middle phalanx of the middle finger, an area known to be very sensitive for warm sensations. The average standard skin temperature was 33·2° (32·7° to 34·0°) and the standard test was, as before, 40°. The result of the two series are graphed in fig. 1. It will be noted that two experiments give negative values to the equivalent stimulus.

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This is, however, merely a consequence of statistical inaccuracy. The two series of observations are so familiar that they may be considered together.

The calculated variance of these data are in general of the order of 1°. In one experiment, however, at an initial temperature of 20·7° the variance was 9°. In another experiment at 27·2° the χ^2 test indicated a lack of homogeneity. Both of these results, though not otherwise discrepant, are excluded. The presence of persistent sensation of cold and heat at the extremes of the temperature range seemed to have singularly little effect on the statistical precision of the results determined at these levels, but because of the intense persistent background sensations of cold at low temperatures, and of heat and pain at high, from the wide area of the forearm it was not possible to work much outside the range of the initial temperatures given in the graph. The number of the experiments is 61 based on the total number of recorded observations of 4,255.

If these results be compared with those of Hahn, they seem at first sight to support his conclusions with the exception that the line representing the course of the equivalent stimulus would strike the zero line at about 38° instead of 33·5° as observed by him for the threshold stimulus. On closer inspection, however, it is apparent that all the data can be represented by a line running slightly convex to the abscissa. There is here no justification for dividing the phenomenon which they represent into two separate ranges as was done by Hahn. The nature of the relationship becomes clear when the logarithms of the equivalent stimuli (excluding the two negative values) are graphed against the initial temperatures. They lie along a straight line. The explanation of this graph is that the process of excitation of warmth depends upon an exponential process, and that any temperature change which produces in the same time the same amount of change in this exponential process causes a sensation of the same intensity. It can scarcely be doubted that if the threshold stimuli, as collected by Hahn, were examined in the same way over the entire course, they too would show a correspondence not to two straight lines intersecting one another at 35·5 but a curve of the same form as that now obtained but running at a lower level. The Arrhenius equation which represents the influence of temperature on chemical reactions is of this exponential form, and the value at any temperature is related to the proportion of molecules with an energy above a minimum level. It seems likely that there intervenes in the end-organ between the temperature change and the discharge of nerve impulses a process of this kind, but nothing can be said of its nature except that it is not the ordinary process of biological oxidation, which follows a more complex course.

This result appears to lead to a satisfactory and uniform explanation of the known facts of the sensation of warmth. There is no sensation of

heat in the Weber experiment on removal of the cold object at a low temperature because a large change in temperature is necessary to produce an adequate change in the exponential process. At high temperatures, on the other hand, a very small increase will produce such a change. As the skin temperature is not absolutely steady (Oppel and Hardy, 1937) small changes which are of no significance when the temperature is normal or low become adequate when it is high and so produce an intermittent sensation of warmth, or, when the area is large, one which is, in effect, uninterrupted. Even when the recorded temperature is steady it is to be remembered that temperature is a statistical phenomenon, and that in a microscopic area, such as portion of a surface in an end-organ, "Brownian" variations of temperature must occur which may on occasion, when the average temperature is high, result in changes in the exponential process adequate to discharge nerve impulses. It will be noted in the graph of the logarithms of stimuli in fig. 1, that at about 35·0° the variance becomes increased. This is in accordance with theory, as at some point on the rising scale of temperature spontaneous oscillations must become relatively large—so large indeed that they alter substantially in one direction or in the other the changes superimposed by the stimulus and so increase the variance. The obvious objection to the theory that when these oscillations in temperature are decreased, they should produce also sensations of cold, will subsequently appear to be without significance.

The occurrence of sensation of warmth at constant temperature depends, therefore, it is suggested, on accidental changes of temperature, either slight changes which could be recorded by sensitive methods, or changes related to Brownian movements happening to occur on the reacting area of end-organs. The probability of these occurrences being sufficiently numerous to reach consciousness depends not only on the average temperature at which they happen, which will determine the rates of change they produce in the underlying reaction, but also on the area of the skin under the influence of this average temperature. For the larger the number of end-organs the more likely it is to happen that a sufficient number of them will be affected by the chance stimulation.

On the other hand, a sensation of warmth at a skin temperature so low that none of these accidental changes would produce sufficient alteration in the essential reaction could arise only as a consequence of an imposed gross change in temperature. The effect of this cannot be altogether simple for as the stimulus causes the skin temperature to rise it must also increase the effect of the progressing change: the total effect must be to some extent an integration. But the rate of change of temperature declines so rapidly (Hensel, 1950*a*) that the maximum result must occur at or near the initial skin temperature.

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The Sensation of Cold

In previous experiments on the sensation of cold (O'Connor, 1935) it was found that the "excitability" rose to a maximum at 28° from which point it fell to rise again to an abscissa value of 35°. It appeared then to fall sharply, although the rise may persist to 37°, and concluded with a continuous fall. The series of observations now to be considered was made on O'Connor as subject. The method was in general the same as that used in the experiments on the sensation of warmth. The area of skin used was the dorsum of the right hand between the extensor tendons of the fourth and fifth fingers. The standard test was the corresponding area of the left hand which was maintained at 32·8° (31·5° to 34·2°) and tested with 26°. All the results are entered in fig. 2 with three exceptions.

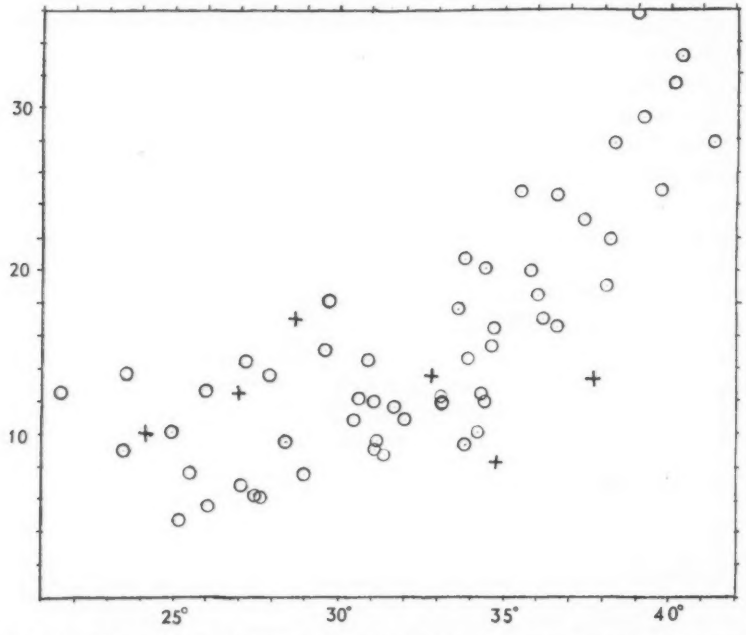

Fig. 2.—The relation between the initial skin temperature and the stimulus required to produce a standard sensation of cold. Abscissa: initial skin temperature. Ordinates—stimulus in degrees centigrade. The circles indicate experiments in which the standard test was 26°; the crosses experiments in which the standard test was 27°.

Experiments were made at 42·4° and 45·8° in which the stimuli had to be so extraordinarily strong that satisfactory results could not be obtained. By extrapolation of the Probit graph the approximate values of the

equivalent stimuli were 45° and 58° respectively, and in one experiment which was done at skin temperature of 32·9° immediately after the second of these just mentioned the χ^2 value indicated lack of homogeneity. In addition to the experiments done with 26° as standard stimulus, six experiments done in an identical manner except that the standard stimulus was 27° are entered on the same record. The total number of experiments was 67. The number of answers analysed is 8,542.

These results confirm in general those formerly obtained (O'Connor, 1935). We find that the excitability (the reciprocal of the equivalent stimulus) rises, with increasing skin temperature to about 26°, falls to about 31° and rises to a new maximum at about 34°, from which it falls steadily to the end. Except that the increase in excitability, in the earlier investigations, was thought to extend in some cases to 37° these results correspond. The most striking feature of this graph (fig. 2) is the maximum of excitability at 34°–35°. If the excitability change with temperature, and if the stimulus depend upon a change in temperature it is likely, as has been mentioned in connexion with the sensation of warmth, that the response to any particular stimulus will be an integration of both processes. It follows from this that the weaker the stimulus, i.e. the less prolonged the change which it produces, the more the variations in excitability will be apparent. In this connexion it may be noticed that the six experiments with a test of 27°, instead of 26°, show much more markedly the increase in excitability in passing from a skin temperature of 30° to 34°. The striking contrast between these results with cold sensations and those with warmth is the fact that the graph of the equivalent stimulus against the initial skin temperature is not continuous. It appears that not one but three phases of change in excitability occur and therefore it would seem three different processes of some kind intervene between recorded thermometric conditions and the excitation of cold sensations from the skin.

Subsequent to the former investigation into the sensation of cold analogies were found between the course of the excitability graph and the oxygen consumption, which made it appear likely that both excitability and oxygen consumption had some common cause or were in some manner related. It subsequently appeared that in the skin the relation of oxygen consumption to temperature could be altered by dressing the skin for some time previous to the observations with a fatty acid (O'Connor, 1943 and 1950). These results were interpreted as showing that the oxygen consumption was dependent on the presence of fatty acids in monolayers, and that the sudden falls at particular temperatures were due to the different fatty acids becoming soluble at these temperatures. Subsequently it was found that this could not be maintained (Armstrong,

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1952). The explanation of the influence of fatty acids on oxidation appears to be connected with the influence exerted by fatty acids in monolayers on the tension of a surface on which they are distributed. If the peculiar relation between oxygen consumption and temperature is caused by such changes in surface tension it seems likely that the similar effect of temperature on the excitability of sensations of cold has a corresponding origin.

The effect of fatty acid on the surface tension of water has been shown by Cary and Rideal (1925) (whose data have been regraphed in fig. 3) to

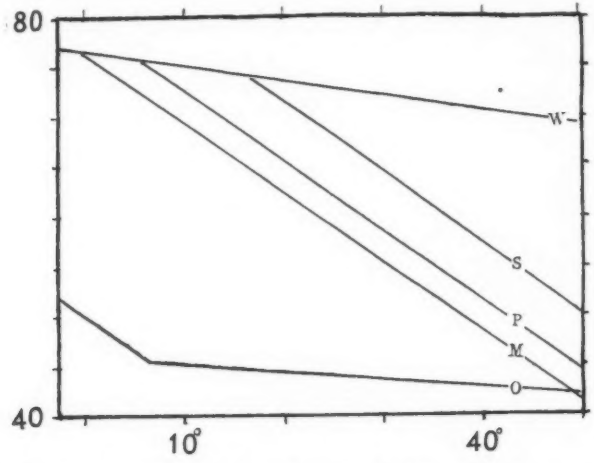

FIG. 3.—Redrawn by permission from Cary and Rideal, 1925. Abscissa: temperature in degrees centigrade. Ordinates—surface tension in dynes per centimetre. The line marked W gives the surface tension for water. Those marked O, M, P and S the influence on it of oleic, myristic, palmitic and stearic acid.

follow simple rules. For example, a crystal of stearic acid on a surface of water does not spread until the temperature has risen to 17°, but above this temperature its spreading results in a continuous uniform fall in surface tension. This fall is reversible on cooling. Palmitic acid follows the same course from about 6° and myristic from about 0°. Oleic acid gives a somewhat divergent result. Cary and Rideal have found that when a mixture of acids is available the fall in surface tension is determined by that acid which produces at that temperature the greatest fall. This rule, however, can hold only when the area is unchanging in size and the acids present in excess. Consider, however, the case where the surface area carries a load, and where the quantities of the acids—oleic, myristic, palmitic and stearic—are limited. At low temperatures the surface tension is determined by the oleic acid; as the temperature

increases the surface tension falls and the area must increase to supply sufficient surface energy to carry the load. The oleic acid being limited in amount will eventually be no longer available to cover a further increase in area. The surface tension will fall from this temperature, but the rate of fall will be slow, until, on the graph, it strikes the line of myristic acid which will then govern the surface tension, but if the myristic acid be in but small amount, as is the case in animal fats, its influence will prevail only over a brief range of temperature. The tension will again change very slowly, until, on the graph, it strikes the palmitic acid line. Palmitic acid, being present in a large proportion, will exercise an effect over a longer change in temperature but must eventually be exhausted and there will be repeated the process which occurred after exhaustion of the supply of myristic acid until the stearic acid intervenes.

On a development of this speculation, the details of which need not now be considered, it is possible to explain the curious course of oxygen consumption with temperature and the influence of the fatty acids upon it. But here we are concerned only with the explanation of the graph of equivalent stimulus for cold against initial temperature. It is suggested that over the range from 26° upwards the excitation is connected with palmitic acid and that at 34° stearic acid intervenes. If this be the case and if the skin be so saturated with one acid that the effect of the others is negligible the graph of the equivalent stimulus against the initial skin temperature should take a simpler form and this form should differ in each case and possibly show, in each, characteristic features. To this purpose experiments were done with stearic, palmitic and oleic acids.

In these experiments the method of measuring the equivalent stimulus was slightly simplified so as to attain more precision without increasing the number of observations. Instead of presenting the standard test and the variable test in alternate order the standard test was always presented first. Again, in the previous experiments temperatures scattered over a wide range were used for the variable test. Statistically many of these were of little value because of their great difference from the finally determined equivalent and the small number at each temperature. The modification now introduced consisted in concentrating on four sets at intervals of 2°. These tests were so selected that they enclosed within them the 50 per cent response. They were presented in as disorderly a manner as possible and 20 tests were made with each. The usual statistical analysis gave the required equivalent temperature.

Stearic acid.—The effect of stearic acid on the relation between skin temperature and the equivalent stimulus was examined in two experiments. In the first of these the subject was McCarthy. The area

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investigated—the dorsal surface of the second phalanx of the middle finger of the left hand—was dressed with stearic acid powder for nine days before the experiment and this treatment was continued throughout the experiment. The standard test was applied to the corresponding area of the right hand which was kept at 37·5° (36·6°–38·2°). As the excitability of the normal skin at this temperature is low the difference of temperature between skin and test had to be greater than in previous experiments in order that a distinct sensation be produced. The selected stimulus was a difference of 20° which was similar to the equivalent stimulus at this temperature in the normal series (*see* fig. 2). It was to be expected that, if the stearic acid produced no effect, the relation between the initial temperature and the equivalent temperature over the entire range would be similar to that shown in fig. 2. This, as can be seen from fig. 4, is not

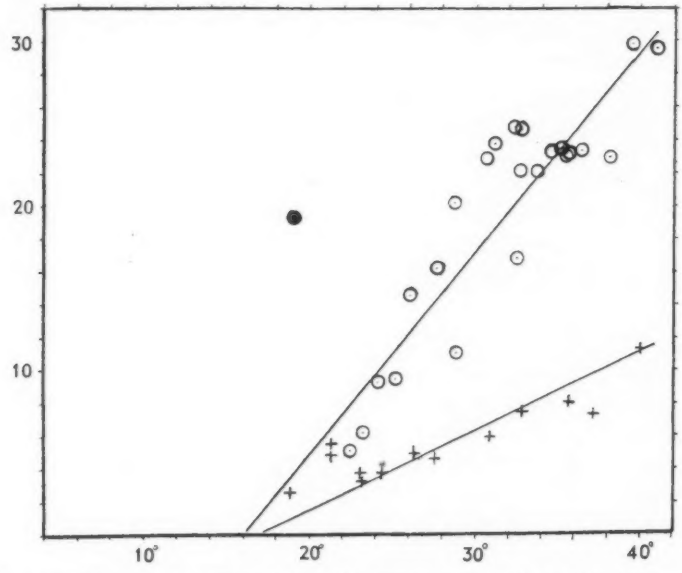

FIG. 4.—The relation between initial skin temperature and the stimulus necessary to produce a standard sensation of cold in skin treated with stearic acid. Abscissa: initial temperature. Ordinates—stimulus in degree centigrade necessary to produce a standard sensation of cold in skin treated with stearic acid. First series of experiments indicated by circles, the filled circle is the maximum stimulus which failed in one experiment to produce any sensation of cold. The second series of experiments is indicated by crosses.

the case. The equivalent stimulus falls uniformly with falling temperature: the increases in excitability at 26° and 34° with the fall between them, which are normally found, are not now visible. In fact the data

appear to lie uniformly along a straight line. The regression line has been calculated—with a small extrapolation it strikes the abscissa at about 16°. Approaching this point, at which the excitability would become "infinity" it was found in one experiment (at 19°) that no applied test—between 0° and 20°—produced any sensation of cold. It would seem that on reaching its maximum excitability the skin becomes inexcitable.

A second experiment with stearic acid was done with O'Connor as subject. The area treated with stearic acid (for nine days) was the middle phalanx of the left index finger. The standard was the corresponding area of the right hand which was held at a temperature of 33·7° (33·3°–35·2°) and tested with 26°. Conditions were thus very similar to those of the main experiment, but it is again found that the relationship between initial temperature and equivalent stimulus is smooth and may be fairly represented by a straight line which when calculated and extrapolated cuts the abscissa at a point near to that found in the first stearic acid experiment. This point is close to the temperature (17°) at which stearic acid in monomolecular begins to spread over a surface. This appears good evidence that in these experiments there is a close relationship between the sensation of cold and the diminution of the spreading of stearic acid on cooling, or with the change of surface tension produced by this with fall in temperature, or with some consequence of this change in surface tension such as a change in area, or change in oxygen consumption.

Immediately following on the first of these stearic acid experiments a short series of observations was made on the same area of skin on the relation between initial temperature and the equivalent stimulus for the sensations of warmth. Stearic acid did not have any obvious effect.

Palmitic acid.—An experiment with this substance similar to that with the second stearic acid experiment was done with O'Connor as subject. In this experiment the area which had been used in the main experiment was dressed with palmitic acid for eight days before investigation. The standard sensation was elicited from the corresponding area of the right hand which was kept at 33·4° (32·0°–34·3°) and tested by 26°. Excluding an observation made at 41·2° we again find (fig. 5) a linear relationship. Extrapolating the fitting line in the same manner as in the stearic acid experiment, but more extensively, it is found to cut the abscissa at 10°. Bearing in mind the extensive extrapolation this is close to the spreading temperature of palmitic acid which (though not so accurately fixed as in the case of stearic acid) is about 6°. Again, there is to be noted the smooth course of the graph, the absence of intermediate maxima and minima and the approximate coincidence of the point at which the

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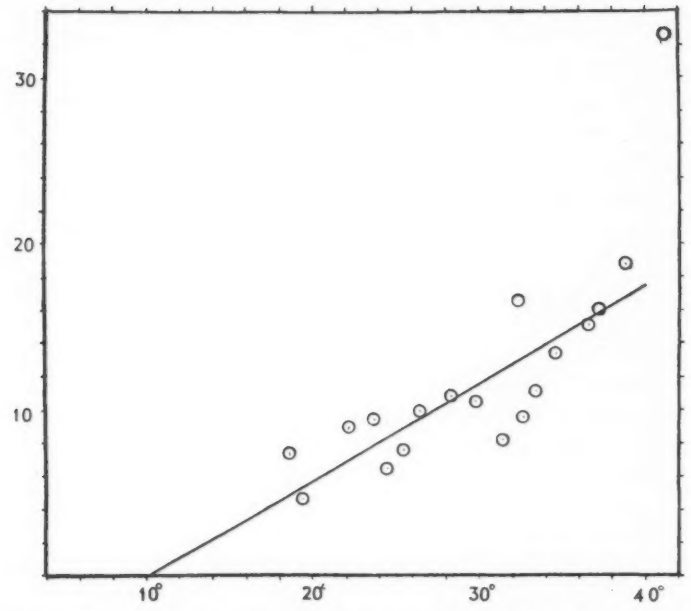

FIG. 5.—The relation between initial temperature and the stimulus necessary to produce a standard sensation of cold in skin treated with palmitic acids. Abscissa and ordinates as in fig. 4.

excitability reaches its extrapolated maximum with the maximum increase on cooling in tension of a surface covered by a monolayer of palmitic acid.

Oleic acid.—Two series of experiments were done with this substance, the first was with McCarthy as subject. The area used was the middle phalanx of the left index finger which was treated for seven days. The standard area, corresponding on the right hand, was kept at 34·6° (33·7–34·8) and tested with 26°. A second series was done with O'Connor as subject. The areas were similar, the treatment lasted for five days and the standard area was maintained at 34·5° (33·7–35·8) and tested also with 26°. The two sets of observations substantially overlap and may be treated together (fig. 6). We again see a smooth course with no indication of the variations in excitability which are characteristic in the main experiment. The portion of the zone of the data which could reasonably be regarded as linear is, however, so brief that an extrapolation to find the intersection with the abscissa would be very dubious. As, however, the relationship between the surface tension effects of oleic acid with those of the saturated fatty acid is remote the fact that no comparison is here possible is not of great moment (*see* fig. 3).

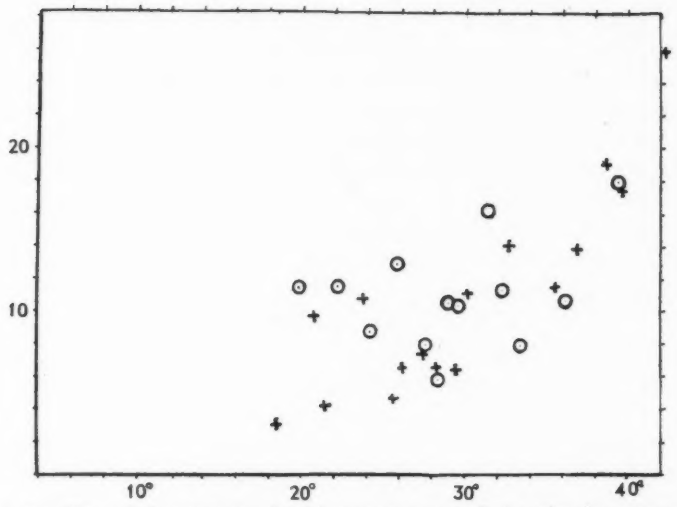

FIG. 6.—The relation between initial temperature and the stimulus necessary to produce a standard sensation of cold in skin treated with oleic acid. Abscissa and ordinates as in fig. 4. The data of two series are represented by circles and crosses.

The alterations produced in the normal relation between initial temperature and equivalent stimulus by treating with these different fatty acids suggest that the sensation of cold is closely associated with the effects of these on surface tension; and that the maxima which appear in the normal course result from the passage of the control of surface tension from one acid to another higher acid, as one after another as the temperature increases they cease to be available in quantity sufficient to produce a further lowering of surface tension. If it could be maintained that the linear relationship between initial temperature and equivalent stimulus which appears under the influence of stearic acid is essentially true and not merely an approximation, it might be argued that the stimulus to cold was the relative diminution in the compression (i.e. the rise in surface tension) produced by a fall in temperature and that so long as this ratio was the same the stimulus to the cold end-organs was the same. It cannot be claimed, however, that this is established, even in the case of stearic acid, because the apparent linearity may be merely an approximate consequence of complex influences. The possibilities of other related changes such as changes in area or changes in rate of oxygen consumption, associated with changes in area, being responsible are not excluded. Complexities may also arise from the fact that the spreading of these acids (and the reverse) are by no means instantaneous and are strongly affected by temperature. Even in microscopic structures where the times, as the areas, are small, these

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rates may be of significance, or become so at low temperatures. But it does appear to be true that the sensation of cold is in some manner associated with the surface changes of tension produced by the changes in temperature on fatty monolayers.

It is characteristic of such surface tensions to be locally unstable. In the cognate case of the soap bubble slight oscillations are indeed essential in maintaining an average stability by reason of the fact that any accidental stretching of a local area by reducing the concentration of adsorbed matter at the particular spot causes a rise in surface tension which restores the balance. Similar slight changes in the surface tension of "the exciting membrane" in a cold end-organ may occur and, when the excitability of the organ is high, be sufficient to result in the discharge of nerve impulses so that without change in temperature there may be a continued sensation of cold. If the area of skin which has been brought to a low temperature be large the chances of excitation become greater, but when the temperature has been raised to some limit, then even if the whole surface of the body is at this temperature the excitability will no longer be sufficient for sensations of cold to arise without change in temperature. The explanation of a continuous sensation of cold constitutes therefore a logical parallel to that advanced for the sensation of warmth.

It will be noticed that if the views put forward in this communication are correct the sensations of warmth and of cold depend not immediately upon changes in recorded temperature but on two opposing and physically different elements in it—kinetic energy and the van der Waals forces. These, respectively, are responsible for the energy which increases with rising temperature and the positive cohesive force which becomes apparent at low temperatures. To examples of these in the skin there is connected the power of originating separated nerve impulses to which are assigned in the sensorium different and positive sensory qualities. Whatever may be thought of the attempt to assess in geometrical terms the intensity of a sensation (*see* von Kries, 1923) any attempt to compare the intensities of sensations of different modalities is futile. Nevertheless there are associated with the nerve impulses which cause these two sensations physical reflex changes which act in the body in opposition to one another: cooling of the skin produces shivering and warming causes reflex vasodilation, the first tending to increase the body temperature and the second to lower it. It has been shown that the intensity of shivering is closely associated with the skin temperature (O'Connor, 1932) and appears indeed to reflect the excitability graph of cold sensations (O'Connor, 1916). It is not extravagant to assume that the vasodilatation reflexes are also related to the excitability for warmth. If this be the case there is a medial temperature, or range of temperature, in the scale of

tolerable skin temperatures at which the two balance. Any departure from this balance will produce an excess of activity of that reflex which tends to restore the skin to its neutral point. It would seem, therefore, that the excitability of the end-organs for warmth and cold from their nature fix the temperature of the skin and consequently of the body at a particular level without any *regulative* intervention of the reflex centres.

Summary

The relation between the initial skin temperature and the applied difference in temperature required to produce a standard sensation of warmth and of cold is investigated.

Warmth.—It is shown that the logarithm of the stimulus falls linearly with rising temperature. This is interpreted as meaning that a process governed by the Arrhenius equation intervenes between the stimulus and the production of nerve impulses and that the same intensity of sensation results from a constant change in unit time in this process. It is shown that the theory adequately accounts for persistent sensation of warmth at high skin temperatures.

Cold.—Confirming former results it is shown that the applied differences in temperature necessary to produce a standard sensation of cold fall to about 26°, rise to about 30° and fall sharply to about 34° from which point it rises continuously with rising initial temperature. Reasons are given for associating this course with the changes in surface tension of a monolayer in which fatty acids can spread. In connexion with this it is found that inunction of the skin with stearic, palmitic and oleic acid respectively causes the graph of stimulus against initial temperature to change to a smooth relationship. In the case of stearic acid the relationship is linear and extrapolation of the line cuts the abscissa at the spreading temperature of stearic acid. In the case of palmitic acid the relationship is linear over the greater part of its course and the extrapolation of the line of relationship cuts the abscissa at temperatures near to the spreading temperature of palmitic acid.

It is concluded that sensation of cold is connected with the rise on cooling of the tension of a surface covered by a monolayer of fatty acid. The origin of persistent cold sensation is considered.

The influence of reflex effects arising from the end-organs of heat and cold on the maintenance of a constant temperature in the body is discussed.

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CEREBRAL LIPIDOSIS: AN ELECTROENCEPHALOGRAPHIC STUDY

BY

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Among the cases routinely examined in the EEG Department of the National Hospital it was noted that several, with the tentative diagnosis of cerebral lipidosis, showed electroencephalograms which seemed to bear a common resemblance one to another, and to be unlike the majority of the EEGs of other mentally deficient epileptic children. Accordingly, it was decided to look for similar appearances in the EEGs of a large consecutive series of patients, paying particular attention to those of patients with cerebral lipidosis, and of children up to the convenient arbitrary age of 10 years.

Material

The period reviewed was two and a half years during which time 7,305 new patients of all ages were seen; the majority of them came from the in-patient and out-patient clinics of the National Hospital, while a large number in the first decade of life came from the Hospital for Sick Children, Great Ormond Street, and a very few from other sources. It is important that the clinical impressions and diagnoses were arrived at by the physicians of the two hospitals independently from the electrical findings. Of the total number 326 were less than 6 years of age and 450 were between 6 and 10 years old, a total of 776 patients. In the first five-year group 291 (89 per cent), and in the second 332 (74 per cent), had epileptic attacks, and of these 623 patients, 105 were considered to show some mental defect.

In looking for EEGs which conformed to the pattern later described all the 776 young patients were reconsidered, while the EEGs of the older patients were also reviewed. We believe, therefore, that the twelve patients to be discussed include all those with EEGs of the type outlined below: it is noteworthy that they were all members of the group of 105 mentally deficient epileptics in the first decade, and that most of the remaining 93 patients in this group showed other clear pathological cause for their disabilities, such as birth or infantile trauma. Also discussed will be 2 older patients with confirmed cerebral lipidosis, 2 patients with probable lipidosis but no fits, and 2 patients with EEGs whose inclusion in the group was more doubtful.

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Technique

All records were made by the so-called bipolar method, using either 14 or 19 electrodes; the former number provided four antero-posterior and four transverse rows, while with the latter there were five antero-posterior and three transverse rows. In all cases the electrodes of a row were equally spaced. Other, non-routine, arrangements were sometimes used in addition. Each of the four machines used had six channels; one was built by one of us, two by the department engineer, Mr. H. B. Morton, and one was a standard Ediswan Mark I. Their response characteristics were essentially similar, and conformed to the standards laid down by the EEG Society. Generally the time-constant of the amplifiers was 0·3 sec. and the high frequency response was level to 75 c/s, but it was sometimes necessary to restrict the band-width in order to obtain a satisfactory record.

In most cases a record, lasting 20 to 30 minutes, was made from the child awake, but repeated records were frequent, sometimes during sleep induced by Seconal. Occasionally, useful records could be obtained only under such conditions.

Results

The type of EEG abnormality which attracted our attention is not easy to describe, or rather, to define in a manner which differentiates it adequately from similar, and possibly allied, appearances. This, of course, is a difficulty familiar to any user of electroencephalography or, indeed, to anyone whose task is the statement of visual impressions in words. It is only necessary to think of the spike and wave complex to realize how inadequately its usual description covers its great variability.

The background activity of the EEGs of these children is usually one of high voltage waves (100–300 μv.) at 1½–6 c/s, mixed in an irregular manner, though the component frequencies may show some approach to regularity. On this background there are many transients varying considerably in form from case to case and particularly in the individual record. Most characteristic are high voltage triphasic waves, sometimes sharp in outline, often with smoothly rounded peaks, having a duration of less than 0·2 sec. No constant focus can be demonstrated for them, most commonly they appear in all leads, and often they are bilaterally synchronous. Although the triphasic form is commonest, greater complexity is frequent, and there is considerable variation in the total period (figs. 1–6).

The features which distinguish these transients from other spike-like forms are their irregular recurrence, their lack of any fixed focus and, in particular, their lack of any constant relationship to the slow waves. Even when they recur more rhythmically, as they sometimes do, it is without any appearance of locking into the slow background activity. In some cases of idiopathic epilepsy there are "formes frustes" of bilaterally

synchronous spike and wave complexes which, in distribution and appearance, resemble the transients described here, but in such cases there is a more constant relationship of the spikes to the slow waves, and overt spike and wave complexes are liable to appear, particularly on overbreathing: furthermore, the background activity in such cases is commonly not very abnormal.

Some of our patients had myoclonic jerks intermittently associated with the outbursts in the EEG, which latter showed no obvious variation in form corresponding with the presence or absence of a jerk. The transients were similarly unresponsive to various painful and startle stimuli, which sometimes cause increase in activity of this sort (Dawson, 1947).

Sleep came spontaneously to one child, and in others it was induced with Seconal, without abolishing the typical features (fig. 4), although their form might be modified. Arousal stimuli were without significant effect and overbreathing also only modified the background in the manner to be expected at this age. In cases where the EEG was repeated, sometimes over a period of months, the records tended to show constant features, though with minor variations, and a temporary disappearance of the characteristic changes was noted in one case.

To provide a clear picture of our 12 patients would require a detailed clinical history of each. In the interests of brevity only the minimum details are tabulated, a method which seems permissible in a paper not primarily concerned with the clinical aspects of the subject. It should be emphasized, moreover, that the authors had no part in deciding on the diagnoses, which were little, if at all, affected by the electrical findings.

Comment

It will be seen from Table I that there are 12 patients between the ages of 18 months and 8 years who present somewhat similar clinical features, and also have EEGs which we consider to have the special characters described. The presence of cerebral lipidosis was confirmed by autopsy in Cases 1 and 2 (figs. 1 and 2) and was clinically certain in Case 3 (fig. 3), in which the characteristic macular changes were seen. Despite the absence of the latter in Cases 4, 5 and 6, the clinical impressions were that these also were cases of lipidosis (fig. 4). In Cases 7, 9, 10, 11 and 12 the diagnosis was the non-committal one of "epilepsy with mental defect," which might be merely an admission of failure to reach a definite conclusion at that time; a diagnosis of cerebral lipidosis is certainly entertainable in all these cases (fig. 5). In Case 8 the history gives some reason to think that birth injury was the starting point of his troubles, although there is little evidence of such an injury to be

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		Onset		First seen					Clinical
	No.	Age	Type	Age	State	Fundi	Course	Pathology	diagnosis
1	3308	?	Always backward. Minor fits from 2 years	3½	Mental defect. Minor and some major attacks	Macular œdema and perimacular pigmentation	Progressive dementia. Died at 4½ years	Autopsy: cerebral lipidosis	Cerebral lipidosis
2	8701	3½	Deterioration and epilepsy	4½	Demented. Gross ataxia. Myoclonus	Normal	Died at 4½	Autopsy: cerebral lipidosis	Cerebral lipidosis
3	10482	9/12	Head injury followed by epilepsy	4	*Grand mal*. Demented. Pyramidal and cerebellar syndromes	"Cherry-red" maculæ	Two prolonged remissions	CSF normal	Tay-Sach's Disease
4	9904	?	Always backward. At 3 ceased to walk and had first fit	4	Pyramidal and cerebellar syndromes. Mental defect. Epy.	Normal	Slow deterioration	CSF normal	? cerebral lipidosis
5	10483	1½	Mental deterioration. Ataxia. Fits since 7 years	8	Mental defect. Pyramidal and cerebellar syndrome	Pale discs. Retinal pigment. Maculæ normal	Slow deterioration	CSF normal	Cerebral atrophy ? lipidosis
6	10755	2½	*Petit mal*	3	Myoclonus. Decerebrate attacks. Mental defect. CNS normal	Normal	Slow deterioration	Biopsy normal	? cerebral lipidosis
7	10821	14/12	Akinetic attacks. Myoclonus	18/12	Backward. Major fits. Ataxia	Normal	Rapid mental deterioration	CSF normal	Epilepsy with mental defect
8	11543	4	? birth injury. Always backward. Fits since 4 years	4½	*Grand mal*. Myoclonus. Ataxia. Speech defect. Mild dementia	Normal	Slow progression. Increasing speech defect	CSF normal	? birth injury ? lipidosis (but see text)
9	5134	1	Fits, increasing	5	Defective, noisy, violent. CNS normal	Normal	Slow progression	——	Epilepsy with mental defect
10	9016	2	Fits	3½	Slight mental defect. CNS normal	Normal	Fits controlled	CSF normal	Epilepsy with mental defect
11	10563	?0	Fits since birth, daily	4	Backward. CNS normal	Normal	Progressing slowly	——	Epilepsy with mental defect
12	11345	2	3–4 *petit mal*/day. 1 *grand mal*/week	3¼	Almost speechless. Ataxia	Normal	Progressing	——	Epilepsy with mental defect

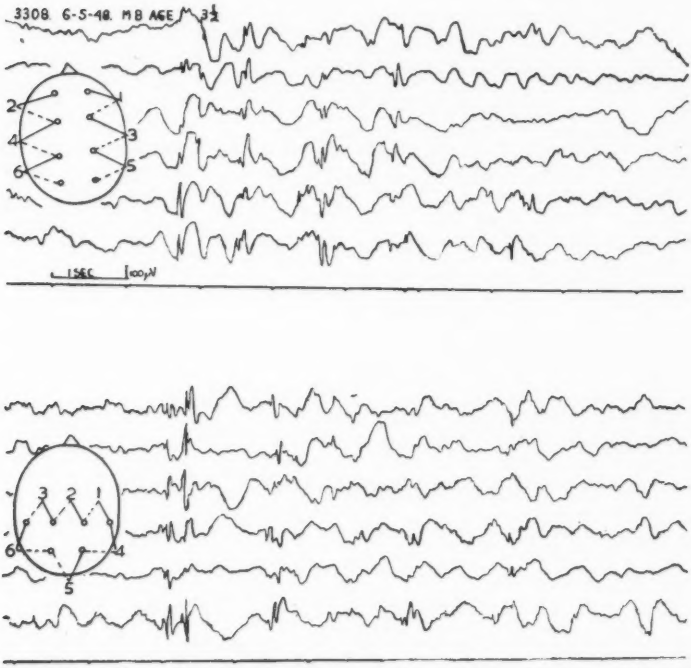

FIG. 1 (*Case* 1).—Male, aged 3½ years. Forceps delivery. Convulsive attacks with loss of consciousness started at 2 years and, at time of EEG, were generalized and occurring several times a day. He was backward and his optic fundi showed macular œdema and perimacular pigmentation. There were no other abnormal neurological findings. About a year later he was admitted to another hospital in, it was thought, the terminal stage of Schilder's disease. Autopsy, however, established the diagnosis of cerebral lipidosis.

obtained from his clinical state. The EEG is more equivocal than those of the previous cases and shows some resemblance to the "spike and wave variant" (fig. 6). Recent information about this patient, kindly supplied by Dr. Graveson, puts this case in a different category from the others. On reduced medication it seems that his ataxia and speech defect have improved and he is at present regarded as normal, apart from his epilepsy.

It is necessary to discuss briefly 6 further cases not mentioned above, but resembling them in one way or another. First, there are two adult examples of cerebral lipidosis, confirmed by autopsy. In one the onset was at 16 and death occurred at 23, while the illness of the other commenced at 13 and death followed at 28. Both showed progressive mental and physical deterioration and were epileptic. In the first case an EEG was recorded some weeks before death (fig. 7), and in the second case

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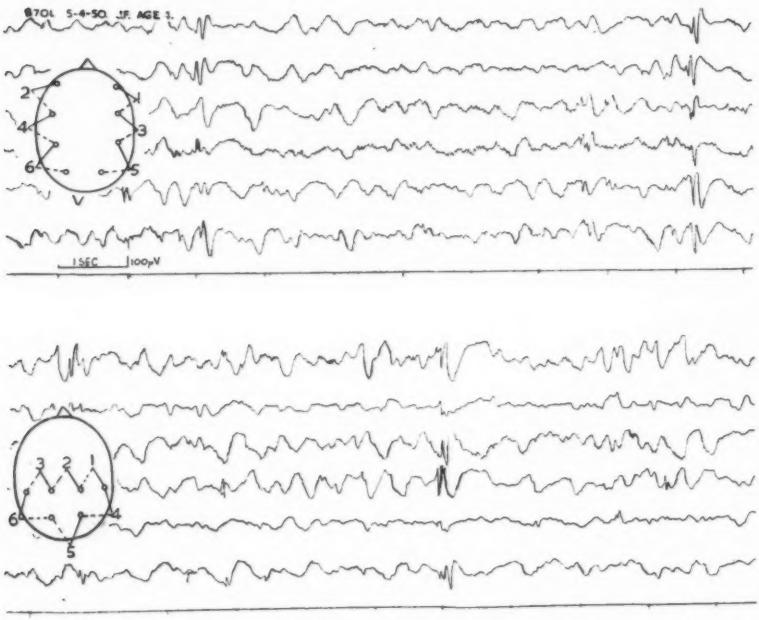

FIG. 2 (*Case* 2).—Male, aged 4 years. During previous eight months there was progressive ataxia and mental deterioration, with an increasing number of fits—major attacks every 2 to 3 weeks, and up to 30 minor attacks a day. He showed gross ataxia, and dementia; there were frequent twitches of the face, trunk and limbs, which could also be evoked by stimuli. The optic fundi were normal.

The child died one month after the EEG was recorded, of broncho-pneumonia. Autopsy disclosed extensive neuronal lipidosis, with greatest incidence in the cerebellum and basal ganglia.

four were recorded during the last few months of life; in both the EEG was abnormal, without the transient phenomena which are the subject of this paper, although the second showed runs of repetitive spikes, associated with myoclonic jerks evoked by various stimuli.

Secondly, there are 2 patients who possibly suffered from lipidosis and who were mentally defective, but who did not have fits. They were, first, a boy of 3½ years who, from the age of 18 months, had failed to advance at the normal rate and whose fundi showed the changes of "early Batten's disease." The second, a girl of 18 months, had a spastic tetraplegia and was blind, though with normal fundi. Her sister died at 8 months, having been blind and also epileptic; unfortunately we have been unable to obtain the post-mortem report on this child. The EEGs of our 2 cases were not normal but did not show the features found in the *epileptic* mental deficients.

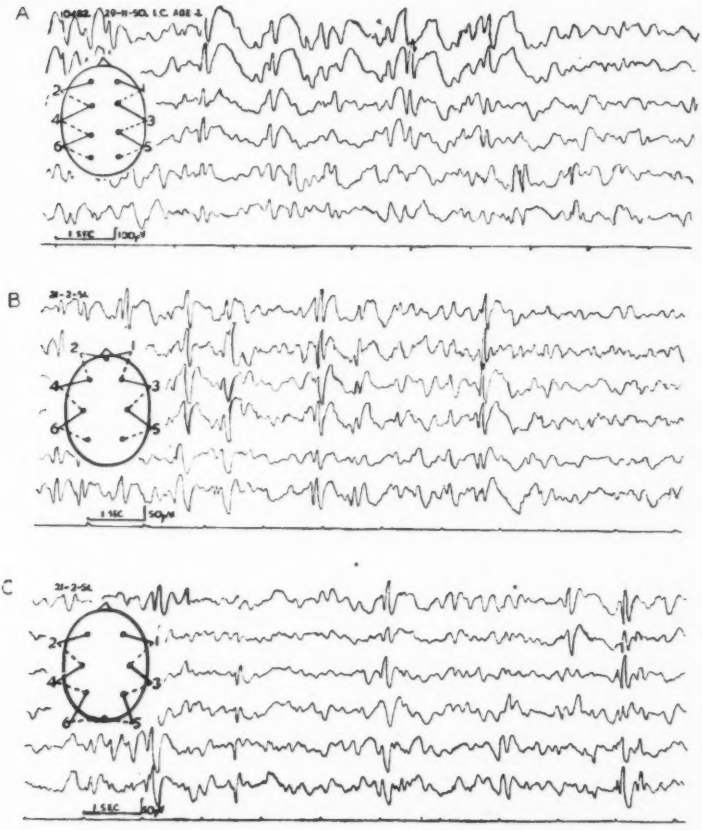

FIG. 3 (*Case* 3).—Male, aged 4 years. Three weeks after a minor head injury at age of 9 months epileptic attacks commenced and rapidly increased in frequency, to become almost daily. After a remission of nearly a year they recommenced. When examined he was speechless and apparently blind; both plantar responses were extensor. The diagnosis of Tay-Sach's disease was based on typical changes in the optic fundi, the maculæ being œdematous with central cherry red depressions.

Before the first record (A) there had been a series of major attacks and, at the time, he was almost unresponsive, whereas he was more fully conscious when the second record (B and C) was made.

Finally, there are 2 cases of some importance in illustrating the borderlands of our EEG picture. Their records show a superficial resemblance to it but, on further consideration, it is obvious that the relationship is much closer to the "spike and wave variant." This is the more interesting because the first of these patients, a mentally deficient epileptic boy of 6 years, had clear indication of infantile hemiplegia, due to birth injury.

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FIG. 4 (*Case 5*).—Male, aged 8 years. Well until aged 18 months, when he ceased walking and feeding himself, and no longer used the few words which he knew. Attacks started at the age of 7, in which he would fall momentarily to the right side; others were longer, with loss of consciousness and jerking of all his limbs. When admitted to hospital he was ataxic and the right plantar response was extensor. There was a divergent squint; vision was present but probably not normal. The optic fundi showed palor of the discs and fine retinal pigmentation. The cerebrospinal fluid was normal. Pneumoencephalography revealed slight generalized atrophy. The diagnosis was cerebral lipidosis.

The records were essentially similar, whether he was awake, asleep after rectal Pentothal (A), or drowsy after oral Seconal (B).

as well as a family history of epilepsy. The second, also a boy of 6 years, had six major epileptic attacks after the age of 2¾. A maternal aunt has had fits since childhood, is mentally defective and has symmetrical adenomata of the face; the history and a photograph suggest the probability that this is a case of tuberous sclerosis; the patient, however, is doing well at school and has no abnormal physical signs. His EEG was finally rejected from the group because, although much of it was acceptable, there were periods when each triphasic wave was followed by a slow wave, and the resulting complexes followed each other more or less regularly.

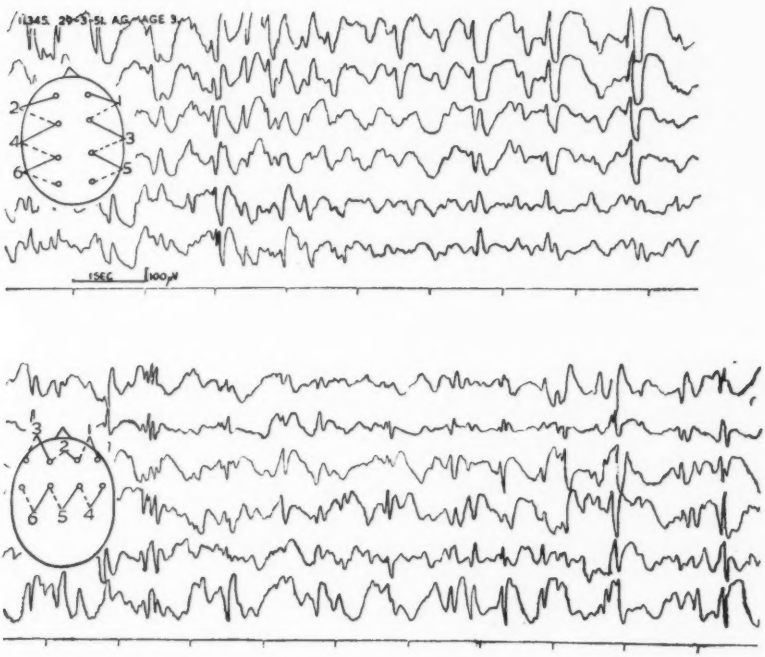

FIG. 5 (*Case* 12).—Male, aged 3¼ years. At the age of nearly 2 years he began to have momentary attacks in which the head dropped forward, he went white and knelt down. These increased in frequency and severity and, at the time of examination, he was having 3–4 *petit mal* attacks a day, and about one major attack a week. He was speaking until shortly after the onset of attacks and then gradually stopped, finally saying little which was intelligible, and not understanding what was said to him. He was unsteady on his feet, often falling, and he was drowsy during the day. There were no other abnormal physical signs.

DISCUSSION

From the EEGs of over seven thousand patients a number have been selected which seem to have a certain common morphology, and none having it have been excluded. It is obvious from the illustrations in this text that the phenomenon which we have attempted to describe is not a clearly defined one, to be recognized immediately it is seen, but few would deny the implication that it is in some way allied to the spikes and "sharp-waves" of other convulsive disorders. It is true that occasionally a focus of spikes or sharp waves may be seen in the EEG of a patient who has never had fits, though we think it happens very rarely to a patient unlikely to have them; that is to say, the spikes in such patients are associated with *potential* epileptogenic lesions. However that may be, our records look like "epileptic" EEGs, and it is of interest that the 2

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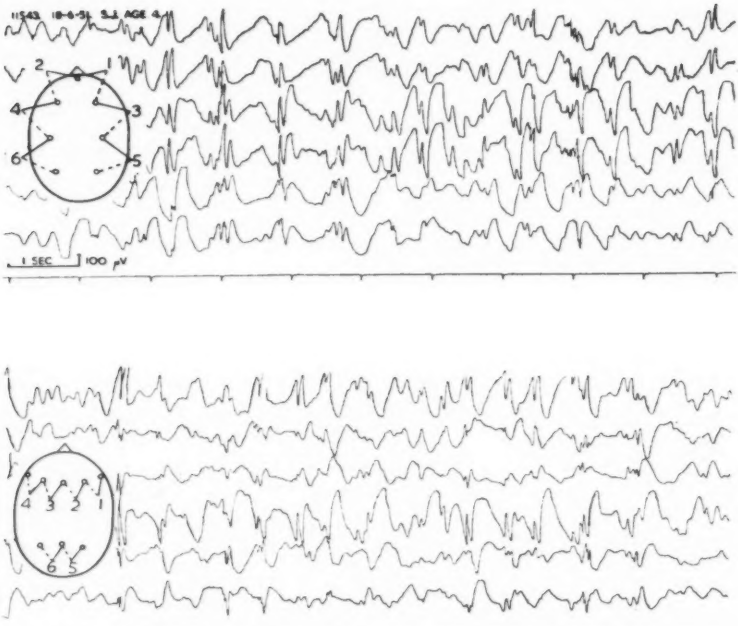

FIG. 6 (*Case* 8).—Male, aged 4 years. Forceps delivery with scarring of the left side of the face and head; there was difficulty in breathing during the first hours. Always a difficult child and a little late in developing. Four months before admission he began to have occasional groups of major epileptic attacks and also frequent minor attacks in which he fell to the ground. Myoclonic jerks would interfere with his walking. At the same time he became ataxic and his speech deteriorated. When examined he was having many myoclonic jerks and minor fits and his speech was unintelligible and becoming worse. There were no definite abnormal neurological findings apart from ataxia. Subsequently his co-ordination and speech have improved, possibly as the result of reducing his medication.

patients with histories and clinical states comparable with those of the other patients, apart from the absence of fits, did not have similar EEGs. On the other hand, failure to find a spike focus in the EEG of a patient with a gross organic lesion causing epilepsy is not at all uncommon, so that, if our transients are indeed allied to "epileptic" spikes, it should be expected that some, otherwise similar, patients would have EEGs without them.

The difficulty, referred to in the previous paragraph, of defining our phenomenon is almost entirely confined to separating it from various forms of spike and wave complex. Figs. 3, 5, and 6 are examples; in the last case the clinical diagnosis was doubtful, though birth injury was finally most favoured. One of the cases described, rejected from our

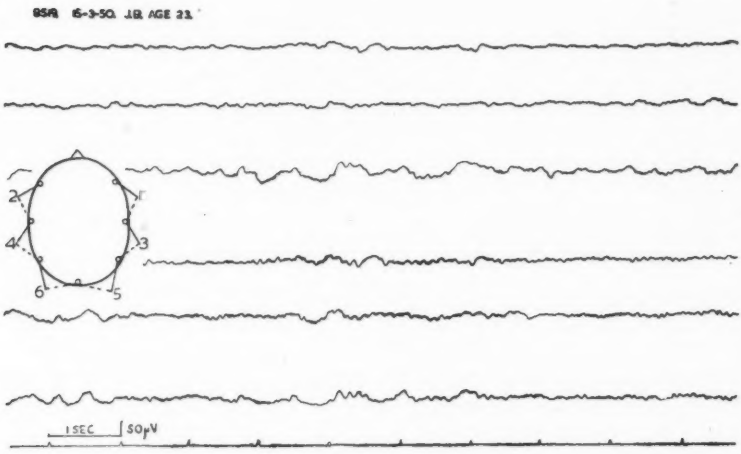

FIG. 7.—Female, aged 23, with a seven years' history of progressive mental deterioration, associated with increasingly frequent major and minor epileptic attacks. Huntington's chorea and Schilder's disease were suggested as possible diagnoses, but biopsy and subsquent autopsy showed diffuse cerebral lipidosis.

main group, illustrates the association of a more definite spike and wave variant with infantile hemiplegia. Lennox and Davis (1950) have recently put forward the view that the slow variant might be an immature form of the 3 c/s spike and wave, and have published figures which show that it tends to occur at an earlier age, to be associated with lower intelligence, and to be more often connected with a definite cerebral pathology. Their results do not seem to offer an answer to the question which they have posed: to do so it would be necessary to observe the change from one form to the other in serial records from the same child; while we have heard of this occurring (Hill—personal communication) we have not seen it in this laboratory. The earlier view of the slow variant was that it betokened symptomatic epilepsy, and, while there may be exceptions, this is usually the case. Its focal form offers no difficulty of recognition, and it is only the generalized, more or less bilaterally synchronous, examples which may be difficult to separate from our phenomenon.

The group of progressive diffuse cerebral diseases which includes Schilder's disease, cerebral lipidosis and subacute progressive encephalitis presents particular diagnostic difficulties, but brief discussion, from the EEG aspect, of some other possible causes of epilepsy and mental defect in children is desirable.

Tumours in young children have similar effects to those in adults, modified by the difference in background, and tending to give rise to

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greater and more widespread abnormality (Hill and Parr, 1950); even where fits occur, transients such as sharp-waves are uncommon.

The sequelæ of diffuse cerebral infections have not received much attention in the literature, but Gibbs and Gibbs (1947) find a close correlation between the persistence of abnormality and the occurrence of fits, and have even noted 3 c/s spike and wave complexes. Such sequelæ are certainly a possible cause of spike-like discharges in the EEG, and not to be overlooked.

The late results of birth and other early injury on the EEG are enormously variable and unpredictable. In infantile hemiplegia there is usually, though not always, a clear asymmetry, and when fits occur there is often a focus of spikes or sharp-waves, less commonly of slow complexes. There are also cases such as the one mentioned above, in which bilaterally synchronous slow spike and wave complexes occur. It is hoped to publish shortly the findings in cases of infantile hemiplegia seen in this laboratory.

To return to the group of progressive diffuse cerebral diseases, since the recognition in subacute encephalitis of characteristic periodic changes in the EEG (Radermecker, 1949; Cobb and Hill, 1950; Martin, Macken and Hess, 1950) we have had a number of patients referred to us with this tentative diagnosis, and as yet no cause has been found of doubt in the specificity of the EEG picture.

In our total series there are 3 children who died of Schilder's disease, diagnosed by autopsy; until death the clinical diagnosis lay in each case between lipidosis and Schilder's disease. The EEGs of these children show only irregular slow waves, without transient activity, despite the fact that fits were a feature of their illnesses. This is contrary to the observations of Gibbs and Gibbs (1941), and Williams and Gibbs (1939) who show EEGs containing high voltage slow waves with spikes; the diagnoses in their cases, however, were clinical and not confirmed by autopsy.

Coming now to consider cerebral lipidosis, the cases mentioned above include all the confirmed examples at all ages, and also all those children under 11 years in whom the diagnosis was at all probable, seen during a period of 2½ years. Our EEG pattern was seen in 3 confirmed, in 3 probable, and in 5 possible cases of lipidosis, but also in 1 case of possible birth injury. It was not seen in 2 possible examples of lipidosis in children, who differed from the other patients in not having epilepsy, nor was it seen in 2 adult epileptics with confirmed cerebral lipidosis.

In the fairly extensive literature on the clinical and pathological aspects of lipidosis we have only been able to find four papers which refer to the EEG. Kornmuller and Janzen (1939) mention a patient with probable

amaurotic family idiocy, later confirmed (*see* Levy and Little), who was epileptic and mentally deficient; unfortunately there is no mention of the age. The illustration of the EEG shows large slow waves, with spikes occurring in an apparently random manner, but is too incomplete for a real comparison to be made with our cases.

Levy and Little (1940) report the case of a boy whose illness began at 5½ years, with the onset of fits at 11 years and death at 12 years. He was mentally defective and blind, with signs of cerebellar and pyramidal involvement. Retinal changes were present. An EEG before the onset of fits was only mildly abnormal, whereas after it there was much more abnormality, with large slow waves and sometimes "spike and slow wave patterns." Again the illustration does not permit adequate comparison.

Lubin and Marburg's (1943) case was a boy of 16 years whose illness commenced at 6 years with progressive mental deterioration and blindness. Fits only appeared a year before death. Autopsy confirmed the diagnosis of juvenile amaurotic idiocy. The EEG, two months before death, showed normal alpha rhythm and "a small amount of random slow activity, greatest in the occipital regions." If the absence of transient changes from the EEGs of our young adult cases is at all a reliable guide it is possible that this patient was already too old to show them.

The case presented by Bjelkhagen (1950) was a Jewish child who died at 2 years, after an illness commencing at 3 months and characterized by fits, including myoclonic jerking, by progressive decerebration, and by blindness associated with typical changes in the fundus oculi. The diagnosis of infantile amaurotic idiocy was confirmed by autopsy. The EEG, four months before death (Dr. B. Holmgren), showed "intense general dysrhythmia of low frequency." The electrode positions illustrated consist of three pairs of electrodes, each pair symmetrically placed astride the mid-line, which is an ideal way of discriminating against bilaterally synchronous activity. Whether or not other electrode positions were used is not stated.

The authors of the first paper were mainly concerned with technique, and of the others with clinico-pathology; consequently the information given on the EEGs is insufficient to allow reliable comparison, and our critical remarks should be taken to express regret rather than censure. All these patients were epileptic and mentally deficient, and, with the exception of that of Lubin and Marburg, were in the same age-group as ours. They may have shown the same phenomenon as did our cases, but the evidence does not permit a definite conclusion.

In effect, then, for both Schilder's disease and lipidosis, the judgment of our findings is little affected by previous published work. We have observed a phenomenon which seems to be almost confined to epileptic

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mentally deficient children. While the numbers involved are too small, and the mutability of the phenomenon too great, to permit any absolute decision, it seems justifiable to state that the presence of these changes makes a diagnosis of cerebral lipidosis very probable, of Schilder's disease unlikely, and of all other causes of mental deficiency with epilepsy improbable, with the exception that, when the wave groups tend toward the slow spike and wave form, the distinction from infantile cerebral trauma is less certain. Conversely, the absence of the phenomenon in repeated records would seem to make lipidosis improbable if the patient is very young, is mentally deficient and has had epileptic attacks. We believe that these EEG patterns offer real aid in the diagnosis of a few cases from the many deteriorated epileptics. The recognition of typical wave-forms in lipidosis and in subacute encephalitis may foreshadow a limited return to the concept of EEG pattern-representation of cerebral disease.

Our thanks are due to the Physicians of the National Hospital and the Hospital for Sick Children whose patients form the basis of this report; and also to the staff of the National Hospital's Department of Applied Electro-physiology, for their constant co-operation.

Summary

A common pattern has been recognized in the EEGs of 12 patients from a consecutive series of 7,305, consisting of the occurrence of random, usually generalized, sharp transients, on a background of generalized slow waves.

(2) These 12 patients were all under 9 years of age, and were epileptic and mentally backward. 3 of them suffered from cerebral lipidosis, and this diagnosis was made in 3 of the other cases, though full confirmation was lacking. In the 6 remaining cases no alternative adequate cause for their epilepsy and mental defect was found.

(3) 2 adult sufferers from cerebral lipidosis did not show this pattern; nor did 2 children who possibly had the disease, but did not have fits.

(4) The EEGs are contrasted with those associated with other diseases causing epilepsy and mental defect in children, particularly subacute progressive encephalitis and Schilder's disease. The scanty literature is surveyed.

(5) It is suggested that the finding of this pattern in the EEG of an epileptic backward child makes the diagnosis of cerebral lipidosis very probable.

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HIPPOCAMPAL AND HYPOTHALAMIC CONNEXIONS OF THE TEMPORAL LOBE IN THE MONKEY

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Introduction

Recent investigations of the temporal lobe have increased our knowledge of different aspects of its activity and have necessitated modifications of our conceptions of the functions of such structures as the hippocampus. It has been reported that the hippocampus, traditionally associated with olfaction, does not receive any direct projection from the olfactory bulb, and that fibres of the olfactory tract reach only the most anterior part of the hippocampal gyrus, which is structurally typical prepiriform cortex. No olfactory tract fibres have been traced to the posterior part of the hippocampal gyrus (entorhinal area of Brodmann) or to the hippocampus itself (Rose and Woolsey, 1943; Fox, McKinley and Magoun, 1944; Le Gros Clark and Meyer, 1947; Meyer and Allison, 1949).

Thus the function of the hippocampus remains obscure, and it becomes important to determine the possible existence of tertiary olfactory paths. These might pass from the prepiriform cortex to the hippocampus directly, or to the entorhinal area and thence by a further relay to the hippocampal formation through the temporo-ammonic tracts of Cajal. Much of the present study has been directed to the investigation of this hypothesis.

The attention of other workers has been focused on certain functional aspects of the temporal lobe. Bucy and Klüver (1940) reported a condition after extensive temporal lobectomy in monkeys which they described as "psychic blindness"—an inability to appreciate the significance of things seen or heard without any measurable defect in actual perception. The emotional response to rage or fear-provoking stimuli was diminished or abolished. Bard and Mountcastle (1948) have shown that lesions in the amygdalæ and hippocampi in cats are followed by altered emotional responses. Blum, Chow and Pribram (1950) found that temporal lobectomy in the monkey led to altered tractability to human handling and also to defective learning ability in problems involving visual discrimination.

Autonomic responses such as blood pressure and respiratory changes

have been reported in monkeys after stimulation of the tip of the temporal pole, the uncus, the anterior cingulate gyrus and the limen insulæ (Kaada, Pribram and Epstein, 1949). These authors suggest efferent connexions to common subcortical centres from all these areas. The tip of the temporal poles in man was stimulated by Chapman, Livingstone and Poppen (1950) with similar results. In this study the existence of temporo-hypothalamic and temporo-frontal connexions has also been investigated.

Material and Methods

Five green monkeys (*Cercopithecus sabæus*) and two macaques (*Macaca mulatta*) have been used. All operations were performed under nembutal anæsthesia. A temporal bone flap was prepared, extending medially to the midline, inferiorly to the infra-temporal crest, anteriorly to the margin of the orbit and posteriorly to the external auditory meatus. With such a wide exposure it was possible to retract the temporal pole laterally and expose the uncus, entorhinal area and adjacent structures with almost no damage to the frontal lobe and minimal damage to the temporal pole. The operations were performed with full aseptic technique. The cortical lesion was made in the first case with the diathermy current but, as this produced extensive necrosis beyond the immediate confines of the cortical lesion, all subsequent lesions were produced by undercutting the cortex with a curved Graefe knife followed by careful suction with a glass-tipped sucker. The latter technique produced a lesion more strictly confined to the region of the operative trauma. In 3 cases the ablation was carried out mainly in the prepiriform region, in 2 in the entorhinal area, in 1 in the superior temporal gyrus and in 1 at the tip of the temporal pole. 6 of the 7 animals were killed five to seven days after operation and the brains later examined by the Glees silver method. In the remaining animal, there was a lesion in the entorhinal area and the survival period was sixteen days. This brain was examined with a modification of the Marchi method. In every case some spread of the lesion into adjacent areas inevitably occurred.

The brains were perfused *in situ* immediately after death with 10 per cent formol saline; they were then removed and fixed in 5 per cent formol saline for a further ten days. Frozen sections were cut at 10–15 μ for staining for degenerating fibres and their terminations by the Glees ammoniacal silver method. At the same levels 25–30 μ sections were stained by the Weil myelin method and also by a Nissl technique, to allow accurate determination of the various cell groups and fibre pathways. Normal serial transverse sections of the whole fore-brain stained by Weigert and Nissl methods were used for comparison. Sections were cut from the opposite unoperated hemisphere at the same level in all cases. Although a true serial picture is not possible with the frozen method, the levels studied were sufficiently close to allow an accurate reconstruction of the course of degenerating fibres to their terminations.

Experimental Results

In the references to the probable cortical areas involved in the lesions, Walker's classification for the frontal lobe and that of Brodmann for the temporal lobe has been used throughout.

Results of Lesions in the Prepiriform (Olfactory) Cortex

Case 1 (*M*85, *Cercopithecus sabæus*).—The lesion destroys a large part of the olfactory cortex of the temporal lobe (fig. 1A). In an antero-posterior

direction it also involves almost the whole of the amygdaloid complex (fig. 1B and C). Only its dorsal part, including the medial and central amygdaloid nuclei, the nucleus of the lateral olfactory tract and the most

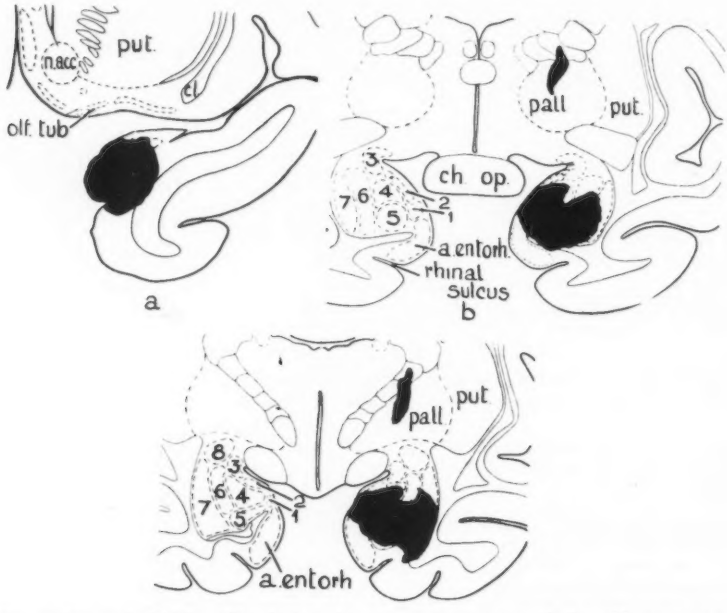

FIG. 1 (*Case* 1, M85).—The lesion destroys a large part of the olfactory cortex of the temporal lobe and almost the whole of the amygdaloid complex. A is at the level of the olfactory tubercle, B at the level of the optic chiasm and the middle of the amygdaloid complex, and C at the level of the caudal part of the amygdaloid formation. Abbreviations: a. entorh. = area entorhinalis; ch. op. = optic chiasm; cl. = claustrum; n. acc. = nucleus accumbens; olf. tub. = olfactory tubercle; pall. = globus pallidus; put. = putamen; 1 = cortico-amygdaloid transition area; 2 = cortical amygdaloid nucleus; 3 = medial amygdaloid nucleus; 4 = accessory basal amygdaloid nucleus; 5 = medial part of basal amygdaloid nucleus; 6 = lateral part of basal amygdaloid nucleus; 7 = lateral amygdaloid nucleus; 8 = central amygdaloid nucleus.

dorsal part of the baso-lateral group, have been spared. The principal lesion in the uncus has spread to a slight extent into the entorhinal area and into the anterior hippocampus itself. Additional lesions are present in the frontal cortex in areas 44, 46, 12, 8 and 9 (Walker) and there is a deep lesion in area 18 (Brodmann) burrowing forward for some distance. A softening in the globus pallidus extends into the internal capsule. On the contralateral side, there is a circumscribed lesion in area 8.

Secondary degeneration.—The lesions are very extensive and widespread, therefore the negative evidence provided by this experiment is

emphasized and is regarded as of considerable significance. Any secondary degeneration which is obviously related to the additional injuries has not been described.

Hippocampus: Apart from localized reaction to the direct injury in the anterior tip of the hippocampus, no fibre or terminal degeneration was found in any part of the hippocampal formation or in the entorhinal area.

Stria terminalis and hypothalamus: Fibres of the stria terminalis are degenerated on the operated side. The different components are difficult to distinguish as they go forward above the internal capsule. At the level of the crossing of the anterior commissure (fig. 2) the stria terminalis

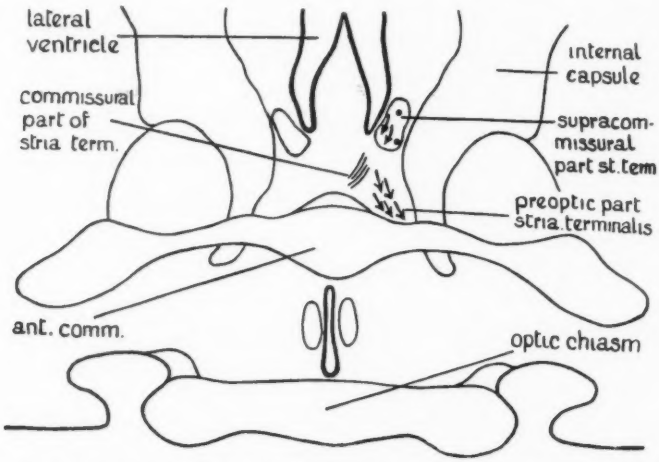

FIG. 2 (*Case* 1, M85).—A section through the hypothalamus at the level of the anterior commissure. In this and subsequent diagrams degenerating fibres are indicated by arrows and degenerating terminals by dots.

subdivides and a hypothalamic bundle (or preoptic bundle of other authors), a commissural, and a supracommissural bundle have been identified in normal material. In this experiment the hypothalamic bundle is completely degenerated, the supracommissural bundle only in part, and the commissural bundle has remained normal. There is severe terminal degeneration in the bed nucleus of the stria in this and in the next level immediately posterior to the anterior commissure (figs. 2 and 3). The degenerating fibres of the stria terminalis, lying now between the internal capsule and the descending columns of the fornix, can be followed into the anterior hypothalamus. In tracing these fibres to their termination in the hypothalamic nuclei, again more weight should be attached to the negative evidence, for the lesion in the globus pallidus might well

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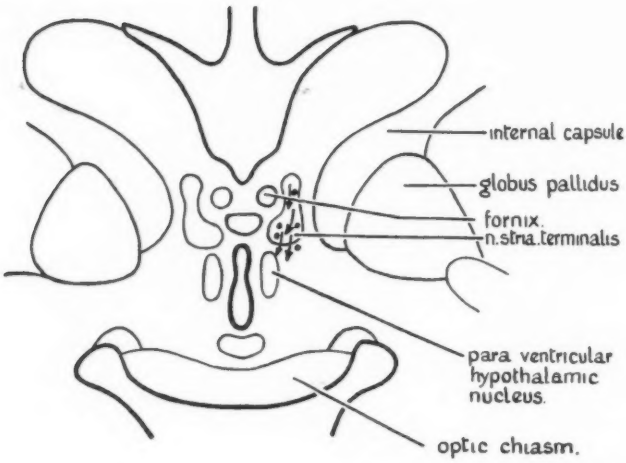

FIG. 3 (*Case* 1, M85).—A section through the hypothalamus immediately posterior to the anterior commissure, showing the course of degenerating fibres of the stria terminalis and the distribution of their degenerating terminals in the bed nucleus of the stria terminalis.

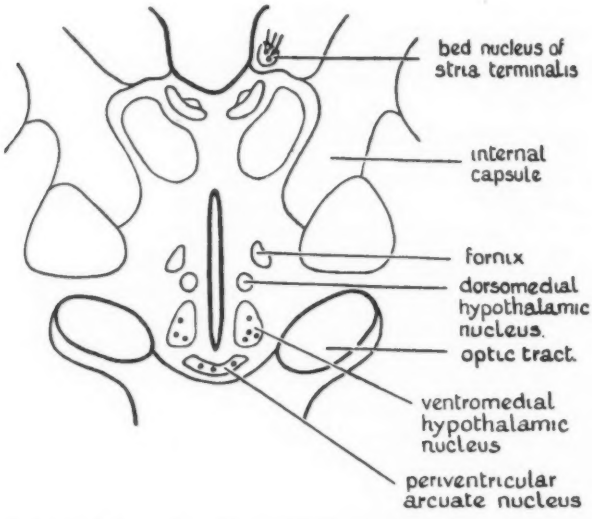

FIG. 4 (*Case* 1, M85).—A section through the posterior hypothalamus showing the distribution of degenerating terminals in the ventromedial and periventricular arcuate nuclei of the hypothalamus. A similar distribution of degenerating terminals in the hypothalamic nuclei was seen in Case 2 after a more restricted lesion.

have severed pallido-hypothalamic fibres, and fronto-hypothalamic fibres might also have been interrupted. In the preoptic region as well as in the anterior hypothalamus, terminal degeneration is diffuse and shows no localization. There is less on the unoperated side. The paraventricular nucleus is normal in both hemispheres. Further caudally (fig. 4) the dorsomedial, ventromedial and periventricular arcuate hypothalamic nuclei show severe degeneration of the terminal plexus. Also in the lateral hypothalamic area there is marked degeneration of fibres and terminals; in this area the degenerating fibres are of thick calibre and probably arise in the globus pallidus. On the contralateral side, degeneration is limited to the ventromedial, arcuate and dorsomedial hypothalamic nuclei and does not appear to be as severe as on the operated side. Caudal to the ventromedial nucleus there are a few degenerating terminals in the medial mammillary nucleus, but elsewhere the hypothalamus is normal on both sides.

Other connexions: The insular cortex of both hemispheres and those levels of the anterior commissure examined show no degeneration. The prepiriform cortex and the amygdala of the contralateral side are intact.

Case 2 (*M*86, *Cercopithecus sabæus*).—The lesion is less extensive than in the preceding experiment, with less incidental damage to other parts of the brain. The greater part of the lesion lies in the limen insulæ, destroying almost the entire olfactory cortex of the temporal lobe (fig. 5A and B). That part of the white matter of the superior temporal gyrus which is adjacent to the lesion is also affected and with it the inferior parts of the external capsule and the anterior commissure (fig. 5C). Although the medial and cortical nuclei of the amygdaloid complex and the nucleus of the lateral olfactory tract have been spared, all the remaining nuclei are injured, but to a lesser extent than in the previous case (fig. 5D). The hippocampal formation has remained completely intact. There are small additional lesions in area 44 going forward into area 12, and in area 4.

Secondary degeneration.—This case is not complicated by additional lesions in the globus pallidus as in the experiment described previously. The lesions in the frontal cortex are very small.

Hippocampus: An anterior level (about 5 mm. behind the lesion), a middle, and a caudal level of the hippocampal formation were examined. There was no degeneration in any of the fibre tracts, and the terminal plexus of all hippocampal and entorhinal regions was intact.

Stria terminalis and hypothalamus: The hypothalamic bundle of the stria terminalis is almost entirely degenerated, very few fibres remaining intact. In the supracommissural component about half the fibres are affected. The commissural bundle could not be identified on the operated

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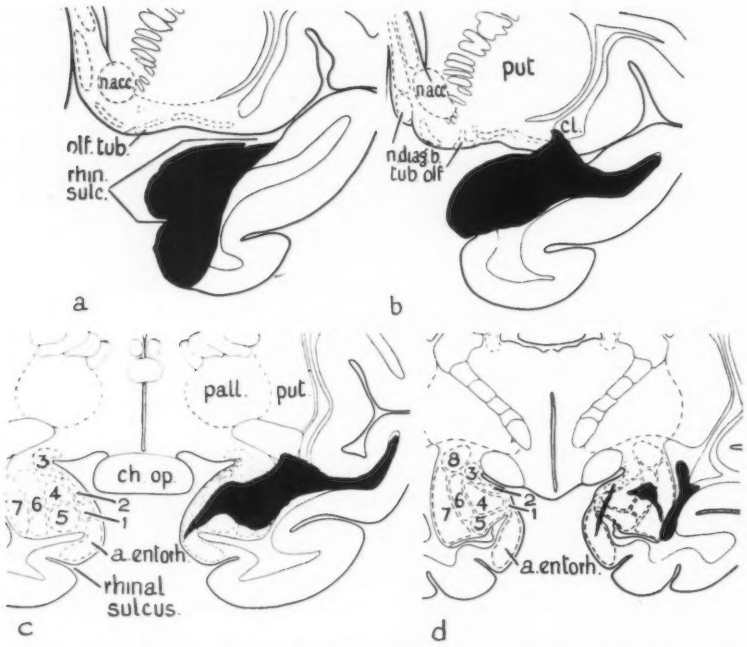

FIG. 5 (*Case* 2, M86).—The lesion is less extensive than in Case 1, and the greater portion of it lies in the limen insulæ, destroying almost the entire olfactory cortex of the temporal lobe. The majority of the amygdaloid nuclei have been injured. A at the level of the olfactory tubercle; B at the level of the limen insulæ; C at the level of the optic chiasm and the middle of the amygdaloid formation; D at the level of the caudal part of the amygdaloid formation. Abbreviations are identical with those in fig. 1, except the following: n. diag. b. = nucleus of the diagonal band; rhin. sulc. = rhinal sulcus.

side. All components of the stria terminalis are normal on the contralateral side. In the stria bed nucleus there is quite severe terminal degeneration which, to a much lesser extent, continues into the preoptic nuclei. Of the hypothalamic nuclei, the ventromedial nucleus shows severe bilateral degeneration of the terminal plexus. It is mainly confined to its lateral parts and extends a little into the periventricular arcuate nucleus. The dorsomedial hypothalamic nucleus is very little affected. It appears therefore that the hypothalamic component of the stria terminalis terminates mainly in the ventromedial hypothalamic nucleus without distributing fibres or their collaterals to other hypothalamic nuclei in its course. (Plate IV, Fig. A.)

Other connexions: The external capsule and anterior commissure, both directly affected by the primary lesion, show evidence of degeneration.

In the latter, at the level of the crossing, degenerating fibres are most numerous at its inferior and superior aspect. In the external capsule, degeneration is confined to its ventral part. Some of these fibres can be traced anteriorly into the orbital surface of the frontal lobe.

The claustrum and the cortex of the insula have also been directly injured and there is terminal degeneration in both these areas, particularly in the neighbourhood of the lesion. However, this finding has to be attributed to the immediate effect of the injury and no conclusion as to the origin of these fibres can be drawn.

The insula, prepiriform cortex and the amygdala of the contralateral hemisphere show no degeneration.

Case 3 (*M87, Cercopithecus sabæus*).—In this brain there is a localized lesion in the prepiriform cortex, which extends into the amygdaloid complex. However, a very extensive softening has occurred from damage at operation to vessels in the lateral fissure (fig. 6A–D). This softening

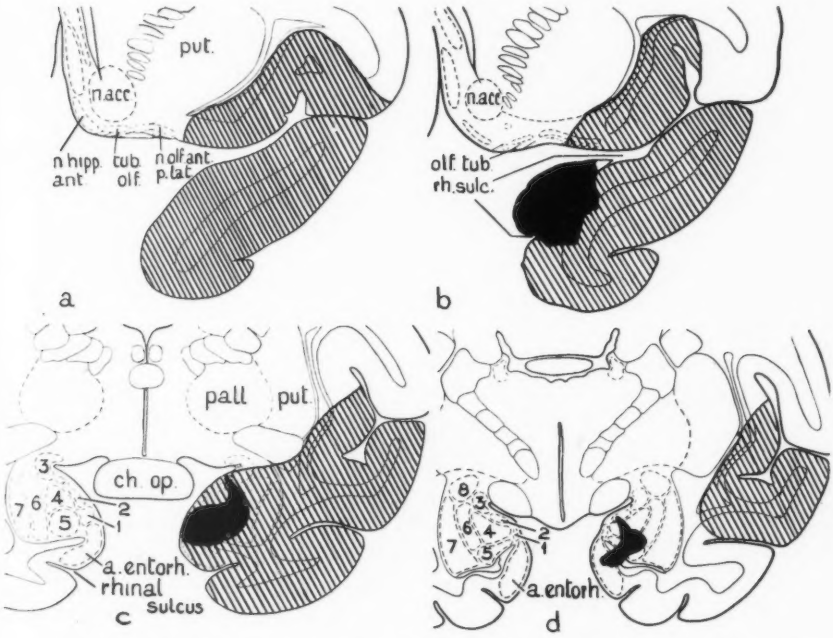

FIG. 6 (*Case* 3, M87).—There is a localized lesion in the prepiriform cortex extending into the amygdaloid complex. Extensive softening from vascular damage in the lateral fissure is indicated by hatching. Abbreviations are identical with those in fig. 1, with the following additions; n. hipp. ant. = anterior hippocampal nucleus; n. olf. ant. p. lat. = lateral part of the anterior olfactory nucleus.

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involves the tip of the temporal pole, the superior temporal gyrus in its whole length, the insula, capsula extrema, claustrum and capsula externa, and much of that part of the anterior amygdala which has not been damaged at operation. A small caudal part of the amygdala is not affected. The inferior temporal gyrus is intact. The ventrolateral part of the posterior frontal lobe has also been affected by the softening.

Secondary degeneration.—Hippocampus: Degenerating fibres sweep downwards in the lateral wall of the lateral ventricle, reaching inferiorly to its floor (fig. 7). They can be traced through the white matter of the inferior temporal gyrus to terminate in the lateral part of the entorhinal area, in that part which corresponds to Lorente de Nó's (1933, 1934) divisions A and B. Degenerating terminals and fine degenerating fibres are present in all layers of the cortex except the first. The medial part of the entorhinal area, which is equivalent to Lorente de Nó's division C or

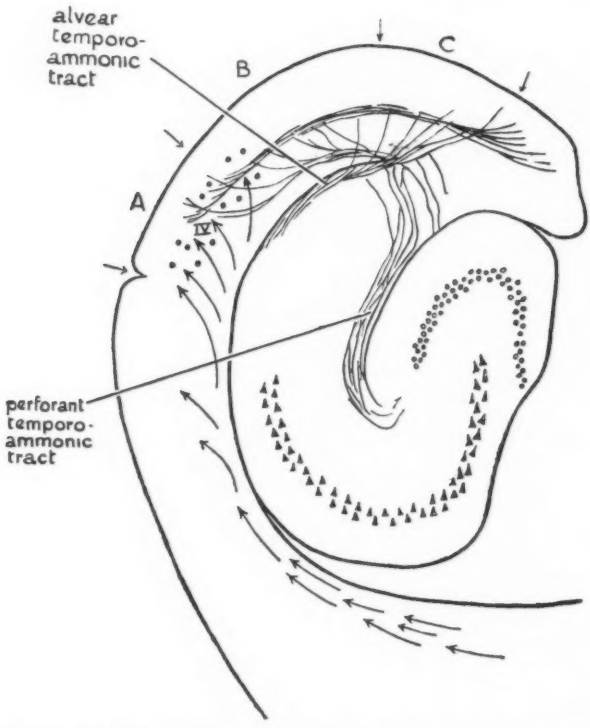

FIG. 7 (*Case* 3, M87).—Degenerating fibres sweeping inferiorly in the wall of the lateral ventricle to terminate in the lateral and middle subdivisions of the entorhinal area.

Cajal's (1911) superior temporal cortex, is free from degeneration. There is no significant degeneration in the rest of the hippocampus.

Stria terminalis and hypothalamus: As illustrated in fig. 4, the degenerated bundle of the stria terminalis is lying in the most lateral part of the stria, almost within the caudate nucleus. The degeneration is unilateral. A stria medullaris component of the stria terminalis has been described in normal material, and in this case the habenula was examined in both hemispheres. No fibre or terminal degeneration was found. In the hypothalamus, again, the ventromedial hypothalamic nucleus shows bilateral degeneration of the terminal plexus; it is more severe on the operated side and extends into the arcuate nucleus. The anterodorsal part of the ventromedial hypothalamic nucleus is apparently normal.

Other connexions: The pericellular plexus of the caudate nucleus is severely degenerated. Because of the extensive lesion, however, the origin of these fibres remains obscure. In the anterior commissure only a few degenerating fibres can be detected; these are lying mostly near its ventral aspect.

In an attempt to discover the area which gives rise to the afferent projections to the entorhinal regions an ablation of the tip of the temporal pole and an ablation of the superior temporal gyrus were performed.

Results of a Lesion in the Tip of the Temporal Pole (Area 38)

Case 4 (M88, Macaca mulatta).—A small crescentic lesion has ablated the cortex at the tip of the temporal lobe (fig. 8). It extends slightly into the superior temporal gyrus; all cortex lying medial to the rhinal fissure, including the prepiriform cortex, the amygdala and the hippocampus, has remained undamaged.

Secondary degeneration.—Hippocampus: Only a very few thick degenerating fibres were found entering the anterior part of the entorhinal area. There was no evidence of terminal degeneration. This result does not indicate that the tip of the temporal lobe is a major projection area to the hippocampal gyrus.

Stria terminalis and hypothalamus: All components of the stria terminalis were found to be intact in both hemispheres. In the hypothalamus there is bilateral terminal degeneration in the caudal part of the ventromedial and in the arcuate nucleus: it is more severe on the operated side. The remaining hypothalamic nuclei are normal.

Other connexions: Possible cortico-cortical connexions of area 38 with the temporal lobe, the amygdala, the insula and the frontal lobe were examined, but no degeneration was found in any of these regions. It

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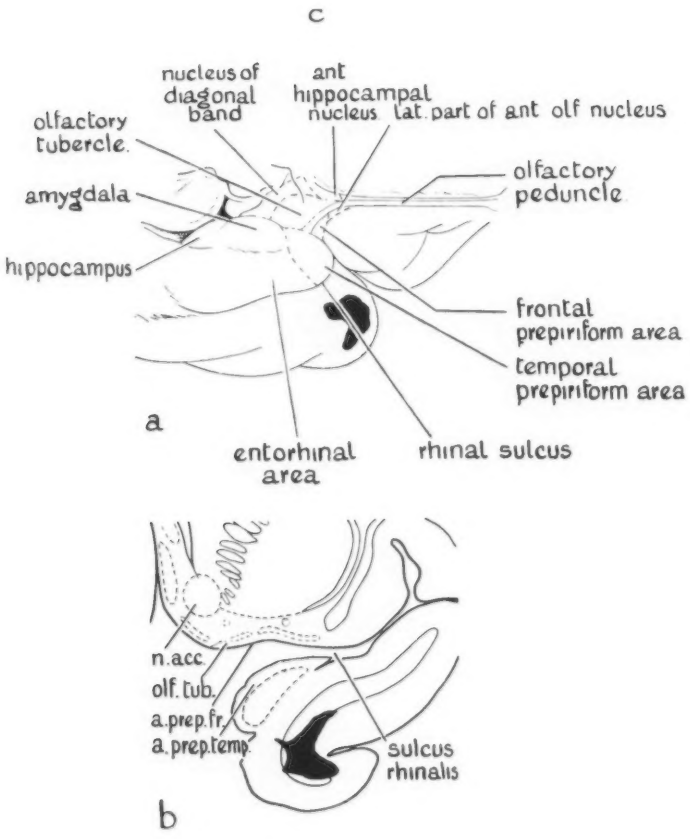

FIG. 8 (*Case* 4, M88).—A small crescentic lesion has ablated the cortex at the tip of the temporal lobe. A shows the lesion as seen from below; B its extent in coronal section at the level of the olfactory tubercle. Abbreviations as in fig. 1, with the following additions: a. prep. fr. = area prepiriformis frontalis; a. prep. temp. = area prepiriformis temporalis.

should be mentioned here that isolated degenerating fibres, which may give positive results by physiological experimental methods, are difficult to pick up among the numerous normal axonal and dendritic arborizations visible in silver impregnated sections of the cerebral cortex.

Results of a Lesion in the Superior Temporal Gyrus (Area 22)

Case 5 (*M*90, *Cercopithecus sabæus*).—The cortex of the anterior half of the superior temporal gyrus between the lateral fissure and the superior

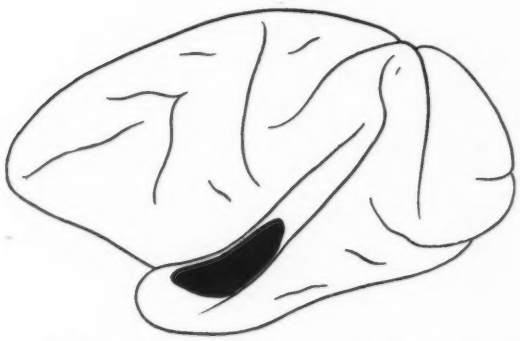

FIG. 9 (*Case* 5, M90).—The cortex of the anterior half of the superior temporal gyrus between the lateral fissure and the superior temporal sulcus has been removed.

temporal sulcus has been removed (fig. 9). Posteriorly the lesion extends to a level immediately behind the lower end of the central sulcus; the tip of the temporal pole is intact. There is a very small contusion over area 44.

Secondary degeneration: No pathway was found in this case from the anterior half of the superior temporal gyrus to the hippocampus or to the entorhinal region. The stria terminalis and all hypothalamic nuclei are free from degeneration. The inferior and middle temporal gyri and the anterior commissure are also normal. There is slight degeneration of thicker fibres in the lateral part of area 13, which can be traced as far as the third cortical layer.

Results of Ablations of the Entorhinal Area

Case 6 (*M*91, *Cercopithecus sabæus*).—The lesion in the entorhinal area is limited to its anterolateral part (fig. 10 a–d). The anterior nuclei of the amygdaloid complex are partly affected, but the lesion tapers into a slit-like incision before the most caudal part of the amygdala is reached. The lesion extends into the white matter of the inferior temporal gyrus and into the inferior part of the tip of the temporal pole. A thin film of blood clot is adherent to the cortex in the lower part of areas 4 and 44.

Secondary degeneration.—Hippocampus: The lesion is confined to the antero-lateral part of the entorhinal area: the medial part containing the dense plexus (which has been described by Cajal in rodents and defined as superior temporal cortex) is very little damaged. From the lesion the degenerating fibres of the temporo-ammonic tract pass through

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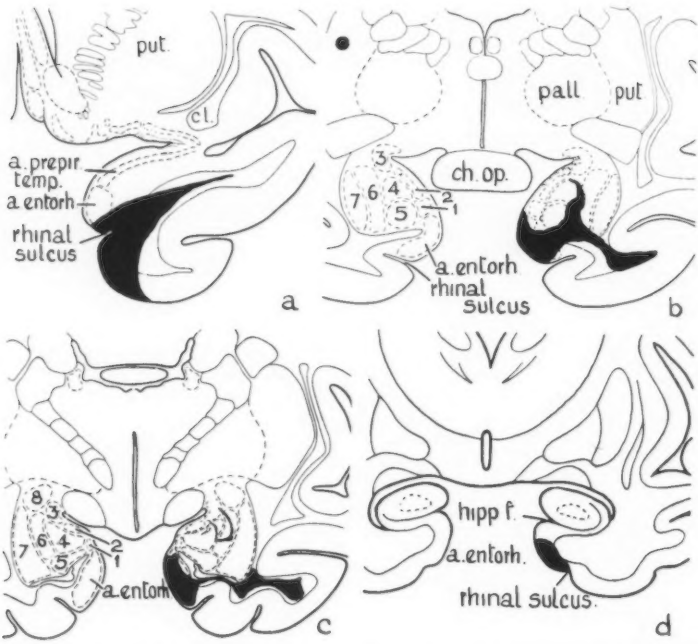

FIG. 10 (*Case 6*, M91).—The lesion is limited to the anterolateral part of the entorhinal area and to the anterior part of the amygdaloid complex. A at the level of the limen insulæ; B at the level of the middle of the amygdaloid formation; C at the caudal end of the amygdaloid complex; and D through the anterior extremity of the hippocampal formation. Abbreviations as in fig. 1. Hipp. f. = hippocampal fissure.

the subiculum (perforating fibres) where some fibres terminate and others pass thence into the molecular or plexiform layer of the hippocampus itself. Most of the horizontal fibres found in this layer are degenerating. These fibres are terminating in the stratum lacunosum of the superior part of the hippocampus. The fibre plexus of the pyramidal cell layer of the hippocampus is free from degeneration, thus suggesting that the synapse is not axosomatic but that the long dendritic shafts of the pyramidal cells make contact with the terminal axonal arborizations of the temporo-ammonic tract. Degenerating fibres in the hippocampus can be traced as far as indicated in fig. 11, the terminals in the stratum lacunosum somewhat further. Other fibres of the temporo-ammonic tract cross the hippocampal fissure to terminate in the superficial or molecular layer of the dentate gyrus. No degeneration was observed in the nerve cell layer. Some fibres of the temporo-ammonic tract also terminate in the subiculum. The presubiculum and the temporo-alvear tract are

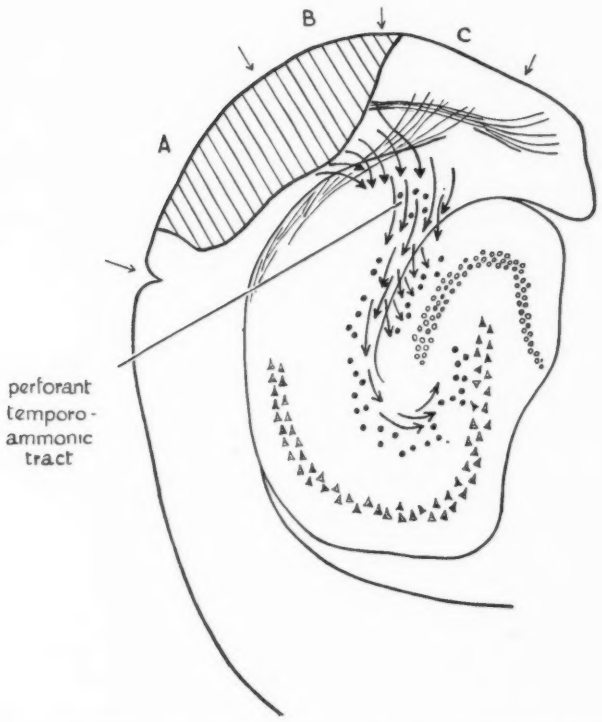

FIG. 11 (*Case* 6, M91).—The lesion in the entorhinal area (shaded) involves subdivisions A and B. Degenerating fibres of the perforant path run through the subiculum to the horizontal fibre layer of the hippocampus and also cross the hippocampal fissure to reach the dentate gyrus. No degeneration is present in the alvear path.

intact. In sections somewhat more caudally (showing the most posterior extent of the lesion which here reaches into the dense plexus of the medial entorhinal area) fascicles of the temporo-ammonic tract penetrating the subiculum are still severely degenerated. Numerous fibres cross the hippocampal fissure into the molecular layer of the dentate gyrus and some terminate very close to the nerve cell layer. At this level degeneration in the hippocampal cortex appears to be less severe than in the dentate gyrus. Sections of the hippocampal formation posterior to the lesion show progressively less degeneration. No degeneration was found in the hippocampus or entorhinal area of the contralateral hemisphere.

Stria terminalis and hypothalamus: All components of the stria terminalis appear to be intact in this case. There is some fine terminal

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degeneration present in the caudal part of the ventromedial hypothalamic nucleus extending into the periventricular arcuate nucleus. (Plate IV, Figs. B and C.)

Other connexions: The orbital cortex of the frontal lobe was found to be intact. The anterior commissure contains some degenerating fibres.

Case 7 (ME, Macaca mulatta).—In this brain the trigeminal nerve was divided at the ganglion and the lesion in the temporal lobe was produced during exposure of the pons. The damage in the entorhinal area extends from the tip of the temporal pole to the posterior end of the hippocampal gyrus. A saucer-shaped depression reaches deeply into the white matter and affects laterally the inferior and middle temporal gyri (fig. 12). The hippocampal formation itself and the amygdala have

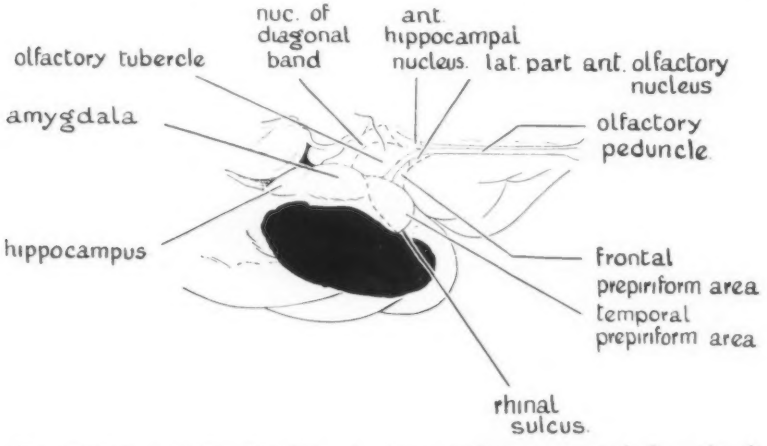

FIG. 12 (*Case 7, ME*).—The lesion in the entorhinal area extends from the tip of the temporal pole to the posterior end of the hippocampal gyrus. The saucer-shaped depression reaches deeply into the white matter.

remained uninjured. In the right frontal lobe there is cortical damage in areas 8a, 8b, and 46 and in the left frontal lobe in areas 9 and 10.

Secondary degeneration.—Hippocampus: In Marchi preparations the temporo-ammonic tract is traced from the lesion into the hippocampal formation. Marchi granules perforate the subiculum in parallel rows (some cross the hippocampal fissure) and collect in the outer layers of the subiculum, sweeping as one broad band of granules into the molecular or superficial plexiform layer of the hippocampus (fig. 13). Marchi degeneration cannot be followed as far as has been described for silver impregnated sections and, of course, the unmyelinated terminals are not visible. In this experiment, the lesion extends into the medial part of

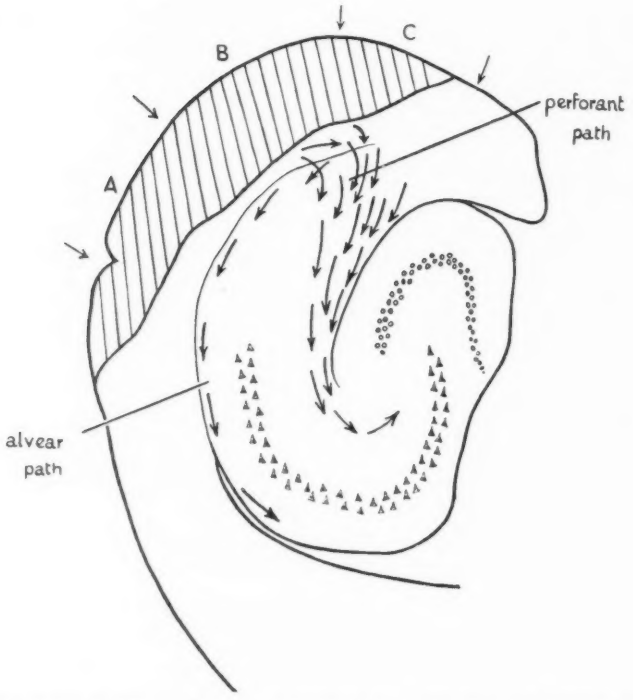

FIG. 13 (*Case* 7, ME).—The lesion extends medially into subdivision c of the entorhinal area (cf. Case 6). Marchi granules are particularly numerous along the perforant path through the subiculum, and extend along the horizontal fibre layer of the hippocampus. The alvear path also shows degeneration granules.

the entorhinal area and some Marchi granules also outline the temporo-alvear path. The hippocampal formation and hippocampal gyrus of the contralateral hemisphere are normal. This case therefore provides no evidence for the existence of a crossed temporo-ammonic tract arising in the entorhinal area. (Plate V.)

There is no Marchi degeneration in the stria terminalis or in the hypothalamus.

Other connexions: From the lesion, which has also destroyed much of the inferior and middle temporal gyri, Marchi degeneration can be traced through the external capsule forward into the posterior orbital surface of the frontal lobe. Serial sections demonstrate that emanating from the lesion a strong fascicle of degenerating fibres outlines the whole of the lateral aspect of the amygdala, joins the external capsule ventrally, moves dorsally and forward within the external capsule and, still passing

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forward, turns towards the orbital surface of the frontal lobe. Numerous degenerating fibres from the inferior and middle temporal gyri pass to the superior temporal gyrus. There is some degeneration in the anterior commissure.

Discussion

The evolutionary modifications occurring in the temporal lobe are considerable. Through rapid growth of neocortex the prepiriform or olfactory area of lower mammals, which occupies such a large part of the ventrolateral region of the hemisphere, becomes greatly displaced anteromedially in primates, and comes to lie on the dorsal surface of the temporal lobe near its anterior end. The displacing mass of cortex appears to be related to functional activities of several kinds, some of which are autonomic, while others are concerned with the perception and appreciation of auditory and probably also of visual stimuli. In view of the varied physiological activities which have been attributed to different portions of the temporal lobe, it is proposed to discuss separately each of the major connexions examined in this study.

The olfactory paths.—There is now strong experimental evidence that the termination of the lateral olfactory tract is limited to the frontal and temporal prepiriform cortex, the cortico-medial amygdaloid nuclei, and the olfactory tubercle. Electrical stimulation of the olfactory bulb by Rose and Woolsey (1943) and Fox, McKinley and Magoun (1944) in carnivores showed such a restricted distribution. Le Gros Clark and Meyer (1947) in the rabbit and Meyer and Allison in the monkey (1949), using the histological method of Glees, confirmed these results and were also unable to find any more extensive distribution to the entorhinal area or any direct connexion with the hippocampus. Our experiments demonstrate conclusively that there is no projection from the primary olfactory cortex (as mapped out by previous workers) to the entorhinal area or to the hippocampus, even when the lesion included almost the whole of the amygdala. Nor were secondary projections seen from this restricted area of prepiriform cortex at the anterior end of the hippocampal gyrus to any adjacent cortical area or to the cortex of the insula.

Allen's (1948) observations, using the Marchi method, are in accordance with the results of these experiments. He could detect no degeneration in the hippocampal formation following removal of the anterior half of the piriform lobe including the amygdaloid complex, and the cells of this part of the piriform cortex showed no retrograde change after hippocampal ablation. Moreover, physiological findings point to the existence of some olfactory integrating centre other than the hippocampus or the entorhinal area, for after electrical single shock stimulation of the piriform

lobe (prepiriform cortex) in dogs Allen (1943) obtained responses from the ventrolateral portion of the frontal area. The same area was found to be essential for obtaining correct conditioned fore-leg responses with olfactory analysers (Allen, 1940, 1941). Unfortunately, the additional injuries to the frontal lobe made impossible any confirmation of this interesting finding in the present series of experiments.

There is limited but clear-cut evidence that, in carnivores at least, olfactory stimuli are perceived after ablation of almost the whole of the so-called "rhinencephalon." In a cat (No. 4) in which almost the entire hippocampal formation, the entorhinal, post-subicular, piriform and peri-amygdaloid cortical areas and all of the amygdaloid cortical areas and all of the amygdaloid nucleus except portions of the cortical and medial nuclei had been removed (in addition to the entire neocortex), Bard and Mountcastle (1948) found that within a week of the ablation the cat was able to find meat placed within a few feet of its nose obviously by olfactory cues.

Afferent entorhinal connexions and intratemporal association paths.— Although the entorhinal area has been regarded by most investigators as an important olfactory centre (Cajal, 1911; Lorente de Nó, 1933, 1934; Brodal, 1947), our experimental material, together with physiological evidence, demonstrates that in the monkey afferent projections to the entorhinal area do not have their origin in the primary olfactory cortex. There is no anatomical information available on other possibly neocortical connexions of the entorhinal region and, despite extensive lesions in the cortex of the temporal lobe, indications for such neocortical pathways are surprisingly inconclusive in our material. In only one case (exp. 3) with extensive damage to the superior temporal gyrus, the insula and adjacent structures, considerable degeneration of fibres was observed which entered the entorhinal area from the overlying white matter and could be traced into the deeper layers of the entorhinal cortex (fig. 7). The region affected corresponds to areas A and B of Lorente de Nó's classification (which gives rise to Cajal's temporo-ammonic tracts) and is lateral to the region occupied by the dense radial plexus characteristic of Cajal's "écorce temporale supérieure." No connexion was found in this case from the superior temporal gyrus to the middle or inferior temporal gyri. A second more restricted lesion in the superior temporal gyrus (M90) did not produce any degeneration in the entorhinal area, while, after an ablation of the tip of the temporal pole (M88), only a few degenerating fibres were seen to enter the anterior part of the entorhinal area from the overlying white matter, but no definite terminal degeneration was observed.

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Recently the problem of intratemporal association paths has been studied by electrophysiological methods, and the findings of Petr, Holden and Jirout (1949) differ significantly from those of Bailey, von Bonin, Garol and McCulloch (1943). Bailey *et al.* reported that in the macaque and in the chimpanzee strychninization of each area (corresponding to Brodmann's areas 20, 21, 22 and 38) fires all that area but does not fire any point in any other area. Projections from these areas to the hippocampal gyrus and hippocampal formation were not recorded.

On the other hand, Petr *et al.* found spikes in the hippocampal gyrus after strychninization of the middle temporal gyrus. Similarly, stimulation of the superior temporal gyrus evoked spikes in the second temporal convolution. The third temporal gyrus fired into the superior and middle gyri and also into the hippocampal gyrus. Bailey *et al.* found no connexions from the tip of the temporal pole to adjacent cortex, but Petr *et al.* after stimulation of this area recorded potentials from the anterior part of the hippocampal gyrus and the uncus. The latter result is supported by Pribram, Lennox and Dunsmore (1950), and to a certain extent by our own material.

Thus from an evaluation of the anatomical and physiological data available it appears that the entorhinal area, and through it a considerable portion of the hippocampal formation, is activated by impulses originating in other than olfactory parts of the cortex.

Entorhinal-hippocampal pathways.—In both our experiments with lesions in the entorhinal area degenerating tracts were traced into the hippocampal formation. The great detail visible in the silver impregnated sections agrees basically with the observations of Cajal and Lorente de Nó on normal material. Cajal (1911) has given a remarkably complete and accurate account of the structure of the hippocampus in rodents and the course within it of the afferent fibres. Lorente de Nó (1933, 1934) has elaborated the account and extended it to the primate brain including man. It is worth while briefly to review the origin and course of the main pathways. Cajal defined three afferent paths to the hippocampus: from the entorhinal area, from the limbic cortex through the cingulum, and through the supracallosal striae (nerves of Lancisi). The afferents from the entorhinal area, first described by Cajal in the mouse, have been reported in greater detail by Lorente de Nó. They form two main paths: the perforant and the alvear. The perforant path corresponds to Cajal's "direct temporo-ammonic tract"; the alvear path includes Cajal's "temporo-alvear" and his "angular" or "crossed temporo-ammonic" path. The latter constitutes the dorsal psalterium, forming a callosal commissure for the entorhinal area. Lorente de Nó concluded from a careful study of

Golgi preparations that each pathway arising in the entorhinal area excites directly the adjacent portion of the hippocampal formation, and that there is a point-to-point projection. He divided the entorhinal area into three projection fields: A, B and C. Field A (the lateral part or area 35 of Brodmann) gives rise to the perforant path, field B (Brodmann's area 28a) to the perforant and alvear paths, and field C (the medial part of the entorhinal area or Brodmann's area 28b) to the alvear path. The perforant path crosses the subiculum into the hippocampus. It is a much larger path than the alvear and Cajal described its course within the hippocampus in detail. He noted that its fibres run horizontally in the molecular or external plexiform layer of the hippocampus. This layer is in direct contact with the molecular layer of the dentate gyrus.

The lesion in the experiment examined by the Glees method (M91) is limited to the anterolateral part of the entorhinal area (Lorente de Nó's field A and part of field B). The ensuing degeneration heavily involves the perforating temporo-ammonic tract. Partly degenerating fibre fascicles perforate the subiculum and follow the curve of the hippocampal fissure into the external molecular layer of the hippocampus. Other fibres cross the hippocampal fissure into the dentate gyrus. From its course in the external molecular layer the tract is seen to give off numerous degenerating terminals to the stratum lacunosum of the hippocampus, the molecular layer of the dentate gyrus and, to a lesser extent, the subiculum. Cajal has shown that extending into the stratum lacunosum and into the molecular layer are the apical dendritic shafts of the pyramidal cells of the hippocampus. The pyramidal cells are thus excited directly by the fibres of the perforant temporo-ammonic tract through an axo-dendritic synapse in the stratum lacunosum and impulses are then transmitted to the fornix.

In the Marchi case (ME) the lesion extends into the medial part of the entorhinal area (field C of Lorente de Nó), and in this experiment some Marchi granules outline the temporo-alvear path. In neither case with an entorhinal lesion was there any evidence for the existence of a crossed temporo-alvear path from the entorhinal area to the contralateral hippocampus, as suggested by Cajal. Allen's studies of hippocampal connexions in the dog point to the hippocampus itself as a source of commissural fibres.

Regarding the functional role of the hippocampus, the experimental evidence available so far supports the conclusion that olfactory sensation is independent of the hippocampus (Allen (1943) in the dog; Penfield and Erickson (1941) in man). Moreover, comparative anatomical studies suggest (M. Rose, 1927*a* and *b*) that the development of the hippocampus

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and the entorhinal area bears no consistent relationship to the development of the olfactory system. Indeed, Rose concluded that the hippocampal cortex is not a reduced region in man, but is most highly differentiated, and certain parts of it he regarded as "a specifically human organ." Papez (1937), in his theory on the mechanism of emotion, believed the hippocampus and its connexions to be essential participants in the expression of emotional experience, and the observations of Bucy and Klüver (1940) and Bard and Mountcastle (1948) seem to support Papez' conclusions. Change in emotional behaviour was one of the outstanding symptoms when the hippocampi were included in ablations of the temporal lobes in monkeys (Bucy and Klüver), and Bard and Mountcastle also observed an increase in pleasure reactions in cats after bilateral removal of the hippocampi together with the overlying temporal neocortex.

Amygdalo-hypothalamic Pathways.—The presence of direct bilateral amygdalo-hypothalamic connexions is a particularly interesting result of this series of experiments. Fibres pass without interruption from the amygdala to the ventromedial and periventricular arcuate nuclei of the hypothalamus of the homolateral hemisphere by way of the stria terminalis. They also reach the corresponding nuclei of the opposite hemisphere, possibly passing through the anterior commissure.

The origin and course of the stria terminalis has been widely discussed in recent years and the different components have been identified mainly in normal material (Johnston, 1923; Young, 1936; Humphrey, 1936). Of the four components (commissural, preoptic, supracommissural and stria medullaris) usually described as emerging from the bed nucleus, only the preoptic bundle is completely degenerated after lesions of the amygdala, and the supracommissural shows partial degeneration. The commissural and stria medullaris components appear normal.

Although our lesions were in no case sufficiently restricted to allow a clear correlation of the various stria terminalis components with the different amygdaloid nuclei, two points emerge. Firstly, the preoptic and supracommissural components of the stria appear to be more closely related to the posterior basolateral parts of the amygdaloid complex than to the corticomedial group. Secondly, the contribution from the anterior amygdaloid area to the stria terminalis is negligible in our material (Case 6, M91).

Our results are in close agreement with those of Fox (1940, 1943). With more restricted lesions he observed that a large part of the stria terminalis (the preoptic and supracommissural components) originates in the basal amygdaloid nucleus, particularly in its caudal end. A stria

medullaris component was not identified in his experiments, nor was he able to observe a commissural bundle even after lesions involving the whole amygdaloid complex. Fox suggests that these fibres are either resistant to degeneration or that, as first suggested by Olive Smith (1930), they might be decussating. The commissural bundle is said to interconnect the nuclei of the lateral olfactory tract of the two hemispheres. As the nucleus of the lateral olfactory trace was always spared in our experiments, no further evidence could be provided to elucidate this point. No contribution to the stria terminalis from the lateral amygdaloid nucleus was found by Fox (1943), an observation supported by Humphrey (1936) in normal material.

In view of the invariably bilateral distribution of the degeneration in the hypothalamus, it is of interest that Humphrey's description of the connexions of the lateral amygdaloid nucleus indicates a possible pathway through the anterior commissure to the hypothalamus of the contralateral hemisphere. He considered that the projection fibres of the lateral amygdaloid nucleus join the anterior commissure and "some fibres may reach the contralateral amygdaloid nucleus; others turn into the preoptic grey, ventral to the commissure." In several of the brains described by us the fine calibre of the degenerating fibres in the anterior commissure is consistent with their termination in the hypothalamus, but the spiral arrangement of the commissural fibres (Fox *et al.*, 1948) makes it difficult to follow the course of a small bundle. The supracommissural bundle of the stria terminalis, which is partly degenerated in brains M85 and M86, can only be traced as far as the vicinity of the anterior commissure and possibly contributes fibres to the latter.

Yet another route to the opposite hypothalamus may be via the fornix bundle. A careful study of the fornix in these cases did not reveal any degenerating fibres. However, the survival period in our animals was only five to seven days, and work at present in progress in this laboratory indicates that the fornix degenerates very slowly and incompletely even when anatomically divided. This matter will be discussed more fully elsewhere (Simpson, 1951).

Stoll, Ajmone-Marsan and Jasper (1951) have recently reported the presence of reciprocal connexions between the tip of the temporal pole and the septal region in the cat, through fibres running in the fornix. Such a pathway may well exist between the amygdala and the hypothalamus. Fibres were also traced to the ventromedial hypothalamic nuclei from the tip of the temporal pole in our material, but degeneration in these nuclei was much less severe than after lesions of the amygdala.

Our material suggests that greater stress should be laid on the part

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played by the ventromedial hypothalamic nucleus as a funnel for impulses from both the amygdala and the neocortex. Le Gros Clark and Meyer (1950) have shown that this nucleus is also the principal site of termination of direct fronto-hypothalamic fibres arising mainly in the posterior orbital cortex (area 13) and in the premotor area (area 6). According to Hess, Brügger and Bucher (1949) this area of the hypothalamus responds to electrical stimulation by a complex syndrome of sympathetic discharge, and, moreover, the cortical areas, both frontal and temporal, from which the ventromedial hypothalamic nucleus receives afferents, respond to electrical stimulation with autonomic effects. Altered respiration and blood pressure has also been stated to follow stimulation of the temporal pole and insula (Kaada, Pribram and Epstein (1949) in the monkey; Chapman, Livingston and Poppen (1950) in man).

In the human fœtal brain, the ventromedial hypothalamic nucleus develops precociously and for a time appears as a relatively large and circumscribed group of cells (Le Gros Clark, 1938; Le Gros Clark and Meyer, 1950). Later its outline becomes more diffuse and thus not so easily definable, probably as a result of the increasing complexity of its fibre connexions. Our sections indicate clearly that the terminations of the various fibres are in different regions of the nucleus. Brockhaus (1942) has shown that the nucleus in the human brain is subdivisible into at least three portions, magnocellular, mediocellular and parvocellular, and this differentiation may well indicate differing cortical connexions.

Summary

(1) After experimental lesions the temporo-ammonic, amygdalo-hypothalamic and some cortico-cortical connexions of the temporal lobe were studied in the monkey. Degenerating fibres and terminals were traced with the Glees silver stain and also by the use of the Marchi method.

(2) No secondary projections were found from the prepiriform (primary olfactory) cortex to the entorhinal area or to other adjacent cortical areas, nor could degeneration be detected in any part of the hippocampal formation.

(3) The entorhinal area is the main source of afferent fibres to the hippocampus. Severe degeneration in the perforating temporo-ammonic tract followed a lesion in the anterolateral part of the entorhinal area. Within the hippocampus the tract runs in the external molecular layer and terminates in the stratum lacunosum and in the dentate gyrus. The synapse with the dendrites of the pyramidal cells of the hippocampal formation is axo-dendritic. Degeneration in the temporo-alvear path only

occurred when the lesion involved the medial part of the entorhinal area. No indication of a crossed temporo-ammonic tract projecting to the opposite hippocampal formation was found.

(4) Vascular damage to the superior temporal gyrus and insula led to terminal degeneration in the anterolateral part of the entorhinal area, the only evidence of an afferent pathway to the entorhinal area found in these experiments. Neither the tip of the temporal lobe nor the superior temporal gyrus projects to the middle or inferior temporal gyri, but a pathway from the inferior and middle to the superior temporal gyrus was found in Marchi preparations. The anterior part of the superior temporal gyrus projects to the orbital cortex of the frontal lobe, particularly to area 13.

(5) The ventromedial hypothalamic nuclei receive fibres directly from the amygdaloid complex and to a lesser extent from the tip of the temporal lobe. The projection is bilateral and approximately symmetrical. As these nuclei have also been shown to receive fibres from the frontal lobe (particularly from areas 6 and 13, from which autonomic responses can be elicited) it is suggested that these nuclei function as a funnel for impulses from both the frontal and temporal lobes, being more important in this respect than the amygdala itself.

(6) The pathways from the amygdaloid complex and tip of the temporal lobe to the hypothalamus have only been partly elucidated in this study. A proven unilateral pathway through the stria terminalis arises mainly in the basal amygdaloid nuclei and the degeneration affects principally the hypothalamic and supracommissural components of the stria. The hypothalamic component has been traced to its termination in the ventromedial hypothalamic nucleus. In all cases the contralateral stria terminalis is normal and no certain evidence has been found of the route by which fibres reach the contralateral hypothalamus. The anterior commissure, the fornix, and the supracommissural bundles of the stria terminalis are suggested as possible paths.

Acknowledgments

We wish to express our thanks to Professor W. E. Le Gros Clark for his constant encouragement and helpful advice throughout this work, and also for performing the cortical ablation in one case. Dr. G. Weddell kindly provided us with the brain studied by the Marchi method. Messrs. E. Thompson, L. Parke, R. Laing and A. Buxton have given valuable assistance in the post-operative care of the animals and in the preparation of the histological material. The study was carried out while one of us (M. Meyer) was in receipt of a grant from the Medical Research Council

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and the other was the holder of a Nuffield Foundation Dominion Travelling Fellowship.

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PLATE IV

FIG. A (*Case* 2, M86).—Amygdaloid-prepiriform lesion. Degenerating fibres in the stria terminalis. × 900.

FIG. B (*Case* 6, M91).—Degenerating terminals around the cells of the stratum lacunosum of the hippocampus. × 1400.

FIG. C (*Case* 6, M91).—Degenerating fibres in the horizontal fibre layer of the hippocampus. × 1100.

PLATE V

Case 7, ME.—Marchi preparation showing the course of degenerating fibres of the perforant temporo-ammonic tract (upper left). The Marchi granules are packed in parallel rows as they run through the subiculum. Their subsequent course follows the sinuous outline of the horizontal fibre layer of the hippocampal formation. × 60.

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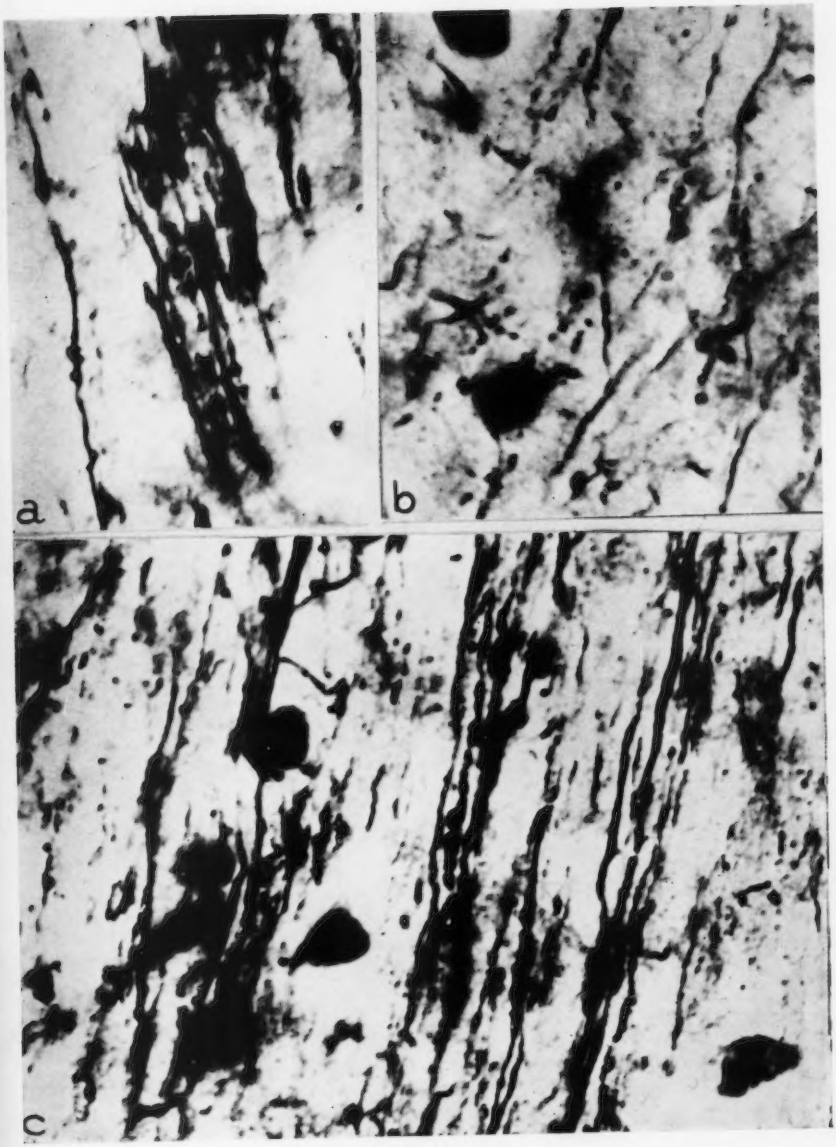
PLATE IV



To illustrate article by W. R. Adey and M. Meyer.

PLATE V

To illustrate article by W. R. Adey and M. Meyer.

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FACIAL REFLEXES

BY

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CONTRACTIONS of the facial muscles in response to taps on the face have been clinically described under a multitude of different names according to the area tapped, the muscles which respond, and the mechanism considered to be responsible. Analysis of the mechanism of the contraction is greatly impeded by the fact that the skin, muscles, and motor nerve fibres are anatomically closely connected and easily moved over the bone, thus transmitting mechanical stimuli over wide areas. Therefore the actual structure stimulated has always been somewhat obscure. Consequently, the winking response to tapping on an area around the eye has been variously classified as a skin reflex (Overend, 1896), a periosteal reflex (Bechterew, 1901; Foerster, 1936), a skin and periosteal reflex (Guillain, 1920), a perichondreal reflex (Simchowicz, 1922), or a bone reflex (Lewandowsky, 1910). Weingrow (1933) and Wartenberg (1945) called it a myotatic or muscle stretch reflex.

The last assumption is a critical point. The existence of stretch reflexes in facial muscles was denied by Sternberg (1893). Sommer (1938) failed to record any action current responses in the orbicularis oculi, orbicularis oris, and buccinator muscles on sudden stretching. Weingrow, in his study devoted purely to a clinical description of new facial reflexes, assumed, without further analysis, that the responses evoked by tapping on the orbicularis oculi and other facial muscles were myotatic reflexes. Wartenberg's similar assumption was based on purely clinical observations. He stated that with a careful tapping technique "one has the definite impression that other stimuli are reduced to a minimum and that concussion and stretching alone are effective." Considering the extremely low thresholds for the wink reflexes evoked by various types of stimuli, such arguments have to be taken cautiously, of which fact also Wartenberg was aware.

In spite of extensive animal investigations an anatomical basis is still lacking for the stretch reflexes and for the proprioception in mimetic musculature. Muscle spindles have not been found (Baum, 1900; Hines and Tower, 1928; Bruesch, 1944), nor have any other nerve endings

suggesting a similar function. Although both the sensory and motor roots of the trigeminal nerve contribute fibres to its mesencephalic root and nucleus mediating proprioception (Corbin, 1940: Corbin and Harrison, 1940; Pearson, 1949), these fibres have not been traced to the facial muscles.

In the facial branches of the seventh nerve the presence of sensory fibres has been shown by the use of chromatolytic methods and degeneration experiments, as well as by studies of fibre count. The afferent fibres have been described as distributed solely to the region of the ear (Rhinehart, 1918; Foley and DuBois, 1943; van Buskirk, 1945), or also to other regions of the face (Davis, 1923; Wakely and Edgeworth, 1933; Bruesch, 1944). Davis described them as pressure pain fibres, Wakely and Edgeworth as muscle afferents. Bruesch suggested that the small calibre fibres traced to free terminals in the adventitia of blood vessels were associated with pain. However, clinical and experimental observations on man suggest some transmission of muscle sense through the seventh nerve (Carmichael and Woollard, 1933).

It is thus clear that more information is needed for the classification of human facial reflexes. In this study the electrophysiological mechanism and the pathway of certain of the facial reflexes is analysed.

Methods

Muscle action potentials were led off by plate or needle electrodes connected to one or sometimes two differential amplifiers operating a double beam cathode ray oscillograph. When one amplifier was used the other beam of the oscilloscope was connected to an oscillator for time recording in intervals of 1 or 2 msecs. The reflexes studied were elicited by mechanical stimulation of the tissues or electrical stimulation of the nerve. The perioral and blink reflexes were elicited by the tap of a light metal rod directly on the skin, or on another short metal rod which slightly stretched the corner of the mouth or a fold of skin in the outer corner of the eye. Other mechanical stimuli were pin-pricks on the skin and light taps on the cornea with a knobbed probe. At the moment of contact with the skin, the cornea, or the other metal rod, the stimulus started the sweep of the oscilloscope which had been suppressed.

The time required to transmit the concussion from the skin to the deeper tissues, such as the muscles, is unpredictable. It varies with the speed and force of the blow. If a light metal rod is used, permitting a high velocity to the blow, this time may be less than 1·5 msec., decreasing to 0·5 msec. Tests show that 1·5–0·5 msec. is the time by which the latency for stimulation of the facial nerve branches by a tap exceeds that of the latency for electrical stimulation on the same point.

In some experiments the stimulus was a puff of air delivered through a Y-shaped tube attached to a rubber bulb which was briskly squeezed. The two shanks of the tube were of different lengths, the shorter being directed against the skin or cornea. The other, as long as the shorter one plus its distance from the target, had a contact in the opening which was broken at the instant that air impact reached it, thereby starting the sweep.

The masseter reflex was evoked by a brisk tap with a reflex hammer on a tongue spatula placed on the lower teeth.

Bipolar electrical shock stimulation of 0·5 msec. duration was also used.

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Results

Electrical response.—A sudden tap on any point within a wide area around the eye evokes at a very low threshold a reflex blink caused by contraction of the orbicularis oculi muscle. The contraction is accompanied by an electrical discharge coming in two groups (e.g. figs. 1A, B, D, E). In the first group the discharge consists of a well-synchronized volley

Fig. 1.—Reflex discharges evoked by tapping. A–E recorded from the eyelid; F from the upper lip. All records except C show two groups of discharges; a well-synchronized volley after a latency of about 12 msec. followed by an asynchronous discharge after a latency of 25–30 msec. Full description in text.

starting about 12 msec. after the stimulus, and lasting 5–10 msec. The second group consists of an asynchronous discharge coming after a latent period of 25–30 msec., and usually lasting 20–30 msec. or more. Both groups are clearly related to contractions of the orbicularis oculi muscle. They are not merely the result of eye movements or electrode shifting, being readily registered by surface electrodes placed on the upper and lower eyelids (see majority of records) and by needle electrodes inserted in the muscle (fig. 1E). In the latter case the typical thin action potentials of the facial muscles may be recorded.

The result is essentially the same, whether the glabella (fig. 1A), the frontal bone (fig. 1B), the nose (fig. 1D), or the zygomatic area (fig. 1E) is tapped. In the past the reflex blink observed has been designated mainly

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according to the area tapped, e.g. the frontal reflex of Overend (1896), the supra-orbital reflex of McCarthy (1901) and Weisenburg (1903), the naso-palpebral reflex of Guillain (1920), the nose-eye reflex of Simchowicz (1922), the nose-bridge-lid reflex of Glattauer (1939). Slight differences in the impulse pattern, according to the point stimulated, may, however, be observed. If, for instance, the glabella is tapped, both responses are well developed (fig. 1A). If then on the same subject the upper part of the forehead is tapped (fig. 1B), the threshold for both responses is somewhat raised, generally slightly more for the first than for the second. The first response is therefore diminished in amplitude relative to the second. This condition is accentuated if the tap is applied to an area as far removed from the eye as the top of the head. The first response may now be missing while the second is relatively well preserved (fig. 1c). This is the cephalo-palpebral reflex of Galant (1926).

If, however, the tap is not too weak, and is not applied too far from the eye, both responses are always present, and were found in all 40 subjects tested. The variation in latency is shown in fig. 2, based on 100 measure-

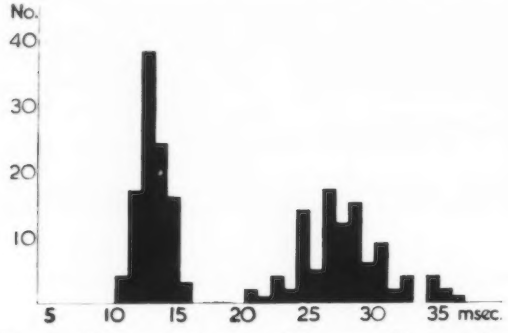

FIG. 2.—Diagram showing the latency of the two different reflex responses evoked by tapping. Recorded from the eyelids.

ments taken in 15 subjects. The mean latency for the first response was 12·5 msec. and for the second, which varied within wider limits, 27·2 msec. The reflexes were evoked by gently pulling a fold of skin in the outer corner of the eye outwards and backwards with a metal rod and applying a brisk tap on it with another light metal rod. The subject's eyes were kept closed. If carefully done no pain is felt, and the noise is not sufficient to elicit a reflex discharge. The usual clinical method of direct tapping on the skin gives the same results.

If the response elicited by the method described is analysed by grading the strength of the stimulus, it is found that in most subjects the threshold for both responses is much the same. Even with a very light tap it is

impossible to get constantly only one response. The result is the same if Wartenberg's (1945) similar technique for eliciting the reflex is used.

In some subjects, however, the threshold for the second response is lower than for the first. A threshold stimulus sometimes elicits both responses (fig. 3A), but often almost only the second (fig. 3B). In other

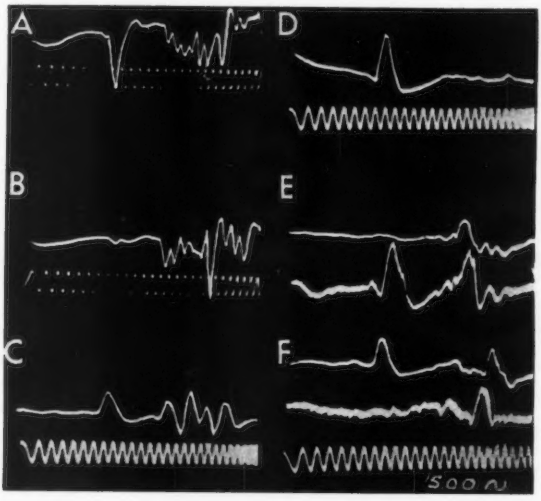

FIG. 3.—Records from 3 subjects: (1) A and B; (2) C and D; (3) E and F. A–D. Threshold stimulus (tapping) tends to produce only the second (B), or only the first (D), response. E and F, Upper tracing in each figure from the left, and lower tracing from the right, eyelid. A tap on the right side (E) produces a right-sided, and on the left side (F) a left-sided, first response, and bilateral second response.

subjects the threshold for the first response is lower. A gentle tap may sometimes evoke two responses (fig. 3C), but often almost only the first (fig. 3D). The independent variations in the amplitude of the two discharges show that two different reflexes are concerned while a purely clinical observation shows only one.

The first response further differs from the second in that it is unilateral, whereas the second response is bilateral. If, for instance, activity is recorded from the upper lids of both eyes simultaneously, and a gentle, sudden stretch is given to the muscle on the right side (the lower recording in fig. 3E), a double discharge with a fully developed first response will be evoked on that side. On the left side, however, only the second response is found (upper recording in fig. 3E). If the stimulus is now moved to the left side, the first response will appear only on that side (fig. 3F, upper tracing) without any electromyographical trace of it from the lid of the

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right eye from which only a second asynchronous response is recorded (fig. 3F, lower tracing). If stronger stimuli are used, the first reflex will be bilateral, probably due to transmission of concussion to the other side.

Although in most subjects the second reflex is already bilateral at threshold strength, sometimes a "local sign" of the reflex is exhibited. In some subjects the reflex at threshold strength is somewhat stronger on the side stimulated, and may occasionally be unilateral, sometimes appearing as fascicular twitchings in the lower lid. However, as soon as the stimulus is raised a little above threshold, the response is distinctly bilateral. If a strong stimulus is used the second reflex may no longer remain localized to the orbicularis oculi muscle. The discharge becomes more widespread and is recorded from adjacent or even more remote muscles in individuals with a lively response.

Other facial muscles, such as the orbicularis oris (fig. 1F) or the chin muscles, readily respond on tapping or stretching at a somewhat higher threshold with a unilateral reflex discharge of the same type as the first response in the orbicularis oculi muscle. After a latent period of 13–15 msec. a well-synchronized volley appears. In some normal subjects the same stimuli evoked even a second asynchronous reflex discharge (fig. 1F) which did not seem to be part of a generalized wink reflex. The threshold was, however, higher than that for the first response. The reflexes of the perioral muscles will be dealt with more fully in a later paper (Ekbom, Jernelius, and Kugelberg, 1952).

Afferent pathway.—Trigeminal rhizotomy abolishes both responses. In 7 patients who had been subjected to complete (2 cases) or almost complete sensory and motor rhizotomy, this was unequivocal as regards the orbicularis oculi reflexes. Case 2 is an example of this. A weak or moderately weak tap on a fold of skin in the outer corner of the eye on the side operated upon produces no response whatever (fig. 4A). A stronger stimulus will produce delayed reflex response, elicited from the opposite side by the spread of concussion, but no early discharge, since this is unilateral (fig. 4B). On the non-operated side a very weak tap evokes the normal double response (fig. 4C).

Tractotomy does not affect the first response, as seen in 4 patients examined. The threshold for the second reflex was raised, but the reflex was not abolished. Apparently, however, in no case was the tractotomy complete. The perception of pain was much reduced, but pain was felt in isolated spots several centimetres apart.

Direct proof that the afferent path for the reflexes examined is in the trigeminal nerve could be secured by electrical stimulation of the trigeminal root in a patient with tic douloureux during operation per-

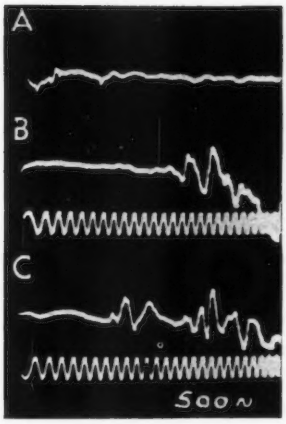

FIG. 4.—Records from the eyelid following trigeminal rhizotomy. A and B, operated side. A weak tap (A) evokes no response and a stronger tap (B) only a second response. C, normal side. A weak tap evokes a double response.

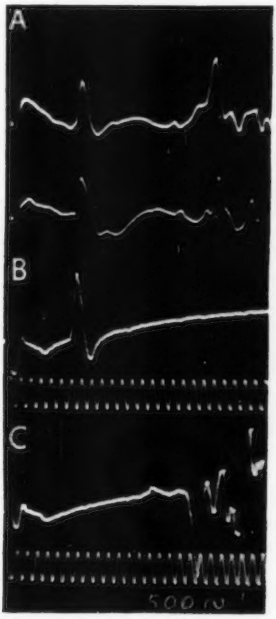

FIG. 5.—Electrical stimulation. A, stimulation of the trigeminal root evokes the usual double response. B and C, stimulation of the infra-orbital nerve through the skin evokes (B) only the first repsonse, and (C), after shifting the position of the electrode slightly, only the second response.

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formed by Dr. Norlén. Since the blink reflexes are rapidly lost during general anæsthesia, the operation had to be performed under local. The dura was opened and the temporal lobe lifted up to expose the middle fossa. The cavum meckelii was then opened, whereupon the trigeminal root could easily be stimulated bipolarly. The typical double response was obtained at a current strength of about 1 mA. (fig. 5A).

Stimulation of the infra-orbital nerve with surface electrodes or needle electrodes inserted in the vicinity of the infra-orbital foramen produces, at threshold strength, sometimes only a first response, sometimes a double response, or more commonly only a second response (fig. 5B and C). The result depends largely on the position of the stimulating electrodes, and careful adjustment is necessary if only the first response is to be evoked. The threshold for eliciting both reflexes is lower than that required for producing a sensation of pain.

Adequate stimulus.—A light prick with a sharp needle or a faint puff of air applied to the skin elicits a very strong second reflex without any trace of the first (fig. 6C). Stimulation of the conjuctiva or cornea elicits

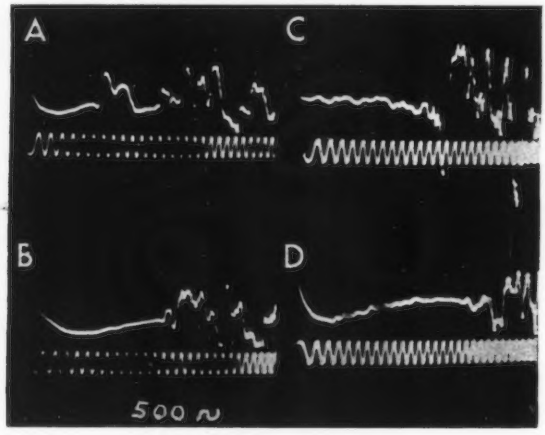

FIG. 6.—Reflex discharges recorded from the eyelid. Tapping with a blunt needle (A) over the orbicularis oculi muscle evokes a double response, and (B) a few centimetres away evokes only a second response. C, a faint puff of air over the muscle evokes only a second response. D, corneal reflex discharge.

only the second response (fig. 6D). Evidently stimulation of receptors for light touch and pain is not adequate for eliciting the first reflex. Greater distortion of the skin or underlying tissues is apparently required. To produce the first response by local distortion the stimulus should be applied over or near the orbicularis muscle. If, for instance, the skin is very

lightly tapped with a blunt pin attached to a flexible wire, a fairly localized distortion is evoked. If the tapping is applied over the muscle, both responses are elicited (fig. 6A), but if applied on a spot a few centimetres away (fig. 6B), only the second reflex appears, with little change in amplitude. Stretch is a very effective method for eliciting the first response. Sudden, slight traction applied to a broad strip of adhesive tape attached to the skin below the eye renders it possible constantly to obtain only the first response, manifested by a faint twitch of the eyelids on the side stimulated. One therefore has the impression that stretching of the orbicularis oculi muscle is the stimulus adequate for evoking the early reflex response although the threshold is exceedingly low.

There is no doubt that pain is an adequate stimulus for eliciting the second reflex. However, a stimulus such as a faint puff of air is also very effective (fig. 6C), although then it is not felt as pain but rather as a touch with a slight tickling quality.

Discussion

Two different types of reflexes are easily produced in the facial muscles by tapping the face. In the orbicularis oculi muscle both are evoked at about the same low threshold. This renders a purely clinical interpretation of the response almost impossible. Wartenberg (1945), by using a careful tapping technique which he assumed reduced to a minimum all stimuli other than that of muscle stretch, evoked a reflex which he described as a blink on the side stimulated, and as a weaker blink on the opposite side. The electromyogram clearly shows, however, that it is not a question of one single reflex, as suggested by Wartenberg, but of two different reflexes on the side stimulated and of one late reflex on the contralateral side, provided a very weak stimulus is used. A stronger tap will give rise to spread of concussion to the opposite side and evoke a double response in both orbicularis oculi muscles. In some individuals a very weak tap will give rise to the first response proper, and a blink is then observed only on the side stimulated. All clinical studies of the blink reflex with a technique based on tapping on an area around the eye have been of a reflex blink composed of at least two different reflexes. To investigate the components separately more refined techniques than those used in purely clinical observations must be employed, although the fact that the first component is unilateral and the second bilateral may be of some help. Other late reflex responses must also be taken into consideration, such as those produced by visual stimuli or when the patient is startled by an unexpected touch or noise.

The first orbicularis reflex is apparently evoked by muscle stretch although this is difficult to demonstrate with certainty owing to anatomical

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factors. The reflex is elicited by stimulation of large, low-threshold fibres, considerably larger, at any rate, than those subserving pain. The reflex discharge is usually a well-synchronized volley similar to that obtained when the facial nerve is stimulated by electric shock. Stretch reflexes in other parts of the body are also accompanied by a discharge of this type (Hoffmann, 1922; Magladery and McDougal, 1950). The reflex elicited by a weak tap over the muscle is restricted to the muscle proper, and thus possesses the restricted distribution of the myotatic reflex (Liddell and Sherrington, 1925). Stronger tapping gives rise to spread of concussion which hampers further investigation of the distribution of the reflex.

More information regarding the reflex may be obtained by comparing it with the well-defined masseter reflex which is a myotatic reflex. The afferent limb of this reflex consists mainly of large myelinated fibres with the perikarya in the trigeminal mesencephalic nucleus (Corbin, 1940; Corbin and Harrison, 1940). The perikarya sends collaterals to the trigeminal motor nucleus (Szentágothai, 1948), thus giving anatomic support to the assumption of a monosynaptic reflex arc which is a characteristic of the spinal stretch reflexes of the cat (Lloyd, 1943). The mean latency for the first orbicularis oculi reflex in 5 subjects was 12 msec., 4·5 msec. longer than that for the masseter reflex which was 7·5 msec. In 3 cadavers the mean length of the efferent arc from the facial nucleus to the upper lid was 25·4 cm., or 15·7 cm. longer than that from the trigeminal motor nucleus to the masseter muscle. The conduction rate of the facial branches of the seventh nerve, measured by stimulating one of the branches at two points 7·5 cm. apart, was found to be 45 metres per second. The conduction rate of the trigeminal motor nerve fibres may be assumed to be the same as that in the proximal part of the facial nerve. In the difference of 4·5 msec. in reflex time, 3·5 msec. may be accounted for by the longer efferent pathway of the orbicularis oculi reflex. To this should be added the difference in conduction time for the afferent path. The pathway from the upper lid over the first trigeminal branch to the pons (10·2 cm.) was 1·2 cm. longer than that from the masseter muscle to the pons. The unknown pathway of the first orbicularis oculi reflex from the root entrance to the facial nucleus may be assumed to be somewhat longer, roughly 2 cm., than the pathway of the masseter reflex from the root entrance to the trigeminal motor nucleus. A 3·2 cm. difference, calculated after a conduction velocity of 70 metres per second (Magladery and McDougal, 1950), would add 0·4 msec. more. This leaves 0·6 msec. which corresponds to the delay of a single synapse (Lorente de Nó, 1938). The calculations, based on the measurement of mechanically induced reflexes with muscle action potentials as index instead of nerve action potentials, should not be stressed too far. From a comparison with the simple stretch

reflex, however, it is clear that the first orbicularis reflex discharge is transmitted through a simple arc. It is, according to existing evidence, compatible with a myotatic reflex.

The second orbicularis reflex, compared with the first, shows quite another picture in almost every respect. The electrically induced response in the muscle is a fairly long-lasting asynchronous discharge. The reflex is bilateral and not restricted to the orbicularis oculi muscle proper, showing widespread responses at stimulus strength above threshold. The reflex time is much longer and more variable. A slower conduction velocity of the fibres of the afferent arc cannot explain the longer reflex time of the second reflex since stimulation experiments show that the fibres are of large calibre and the afferent arc is too short for any minor difference in conduction speed to play any considerable role. The central pathway might be longer, since some part of the reflex is evidently directed over the spinal tract of the trigeminal nerve, but the main difference in time is certainly due to the intercalation of the greater number of synapses. The general characteristics of the second response are the same as those of the conjunctival or corneal reflexes but the latency is shorter (fig. 6D).

Summary

Reflex discharges in facial muscles evoked by mechanical stimulation have been investigated chiefly in the orbicularis oculi muscles. Two different types of reflexes with separate latencies are noted. Stimulation or section of the trigeminal root shows that the afferent paths of both reflexes are to be found in the trigeminal nerve.

(1) The first response is a well-synchronized volley with a latency of about 12 msec. The reflex is unilateral. From a comparison with the masseter reflex it is clear that the reflex discharge is transmitted through a simple arc. It is, according to existing evidence, compatible with a myotatic reflex.

(2) The second response is a long-lasting asynchronous discharge with a variable latency, roughly 21–40 msec. The reflex is bilateral, having no restricted distribution, but shows widespread responses on stronger stimulation. The reflex arc is multisynaptic, and at least some part of it passes over the spinal tract of the trigeminal nerve. Adequate stimuli are pain and probably touch.

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This paper is one of a series presented to Professor Herbert Olivecrona on his 60th birthday by friends and pupils.

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ACALCULIA [1]

BY

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In 1900 attention was first paid to disorders of calculation developing in patients who hitherto had shown no disturbance of their arithmetical faculties. Acalculia was systematically described and named by Henschen (1919) after a thorough survey of the material available. Henschen found that difficulties in the identification and in the naming of printed or written figures and numbers may occur without accompanying disorders of calculation. As on the other hand cipher- or number-blindness may be seen in many cases of acalculia without word-blindness, Henschen assumed that a visual factor, bound up with the occipital cortex, plays a part in calculation. Acalculia was observed in occipital, frontal, parietal and temporal lesions including atrophies, in the absence of aphasia. Henschen, therefore, concluded that the integrity of several areas of the cortex is essential for calculation and that a separate system, independent of the apparatus for the use of language and of music, exists in the human brain. Yet it remains remarkable that as a rule acalculia is associated with "acopia," or the incapacity to copy a text, notwithstanding an ability to read which is impaired but slightly, if at all.

Other neurologists, such as Peritz and Sittig, found acoustic, visual and ideational defects in cases of acalculia. Acalculia naturally implies a disturbance of modern computation, or Western arithmetic. Calculation was formerly regarded as a particular ability of the merchant. Not until the eighteenth century, when children learned tables by heart at school, did arithmetic become a common ability. We visualize the tables memorized in the first school years, when they were learned visually as well as motoro-acoustically. They were recited aloud and with most of us they still resound in our mental ear when we come to use them. Thus calculation is not a primary or biological human capacity, but one which bears in its practical realization the stamp of our cultural configuration.

This means that we are compelled to study the psychology of modern

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arithmetic before facing the problems pertaining to acalculia. Primitive people, as well as children, do not count, but work with sets of objects, with groups—aggregates or manifolds, as they are called in mathematics; they distinguish the relations "bigger and smaller," "more or less" and "part or whole," with the insight that the whole is more than a part. Piaget (1941) observed that children at this stage have not yet the notion of, nor the insight into, quantity, and that the above-mentioned aspects are still qualities. These fundamental qualities are the foundations of calculation, addition and subtraction, and so on.

The conception of number as a cardinal, that is as something belonging to a group as a whole, has, as a prerequisite, the idea of a whole consisting of its parts. A group is counted, the insight being necessary that only one number is the "image" of a given group. Mathematically speaking only one number (that is, one place in the numerical series) represents a given aggregate or set. The irrevocability or unambiguity of the result of counting is its cardinal principle, even of calculation. The mathematician is fully aware of what he is doing in calculation in that he works with aggregates as well as with numerical quantities, and therefore with the symbols used for number-notation. The representation of numeral quantities by words is called numeration; the representation by written signs is called notation. The systems adopted for numeration and for notation do not always agree (or fully correspond) with one another, as for instance in France where eighty is called "quatre-vingts" or "four-twenties."

We use the Hindu system for the notation of numbers, which proceeds by ones, tens, tens of tens, etc. Essential features of this system are:

(1) the limitation of the number of different symbols to ten, however large the number in question;

(2) the use of the zero to indicate the absence of a power;

(3) the principle of local value, by which the value of a digit changes according to its position within a number-notation.

In our notation of natural numbers we thus not only make use of the denary scale but we represent the first nine natural numbers by different symbols, namely, the digits. The ingenious symbol for the zero, the "nought" (0), was devised as late as the seventh century in India; in the Middle Ages it came to Western Europe by way of the Arabs. The zero is no natural number[1] and its symbol therefore does not represent a number, but in arithmetic it is treated like a figure—a fact of the utmost importance. The conception of the zero and the introduction of its symbol made arithmetic as easy as it is nowadays.

[1] From a philosophical point of view "one" is not a number either (Husserl).

Upon the symbols for the first nine numbers and the 0, a logical system is erected for the notation of the higher numbers, beginning with the ten (10). This plural cipher notation proceeds from right to left, and the local value of a digit within a number notation is counted from the right, its place corresponding to the power of the base. The absence of a power within a number-notation is indicated by a 0, which may be called a "place filler."

A number has its place in the set of number names. Man's ingenuity has developed a logical symbolism in the form of sets of symbols, visible numerical signs, that enable him to judge immediately whether the number it represents is lesser or greater than another number, represented by another plural cipher notation, provided that he knows the ten fundamental symbols and the numerical value they represent, as well as the rules governing plural cipher notation. The basic principle underlying this is the isomorphism of the numerals as visible numerical signs with the numbers.

Such a system of symbols manipulated according to certain conventions is called a semantic (or semiotic) system.[1] To handle such a system one must know the elements and the rules of their combination. It is evident that ideational as well as visual factors play a part here.

A patient who does not know the ten basic symbols any longer may suffer from dementia, from visual agnosia or from asymbolia. Inability to handle the plural cipher notation, the patient still recognizing the digits, may be due to visual agnosia or to the loss of insight into the composition of these notations, dementia, or asemasia. Some patients no longer regard a numeral as an entity, for example 286 may be regarded as 2, 8 and 6 or as 2 and 86. The succession or the place-value may have lost its meaning: 26 may be identified as sixty-two: 10 may be one-nought, or 1 or 0.

Our arithmetical procedures are based on the semantic system of number-notation using the Hindu symbols and their arrangement. Clearly in written arithmetic we are not handling numerical quantities, numbers proper, but their symbols—this according to the principle of the isomorphism of both series. Arithmetical operations are free from ambiguity. If we bring the parts of plural cipher notations in relation to each other in the more or less complicated ways we have been taught, we rightly assume that the ensuing symbol is indeed the symbolic notation of the answer, that is, the number wanted or sought. Those skilled in arithmetical operations no longer wonder about the technicalities, and

[1] Other semantic systems include languages, maps, morse and braille signs—such games as cards and chess; signal systems like semaphores, flags, etc.

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forget the painful steps taken in learning the procedures of calculation, as well as the training necessary to handle them fluently.

The process of thought in additions like 378 + 497 is complicated indeed. One must remember that units are added only to units, tens to tens, etc., and hence it is convenient to write units of the same denomination under one another in the same column. The ciphers in each of these columns must be "brought in relation" to each other. Every 10 units of one denomination (like the 10 of 15 in our example) must be "carried" as a unit to the next column, in this case to that of the tens, the same as we "borrow" in subtractions from the cipher at the left side in the minimend if this is necessary. The main arithmetical fact is that we *regroup* the numerical quantities represented by the numbers; e.g. in our example 8 + 7 not as 9 + 6, but as 10 + 5. This is self-evident no doubt, but it is none the less an ingenious procedure.

In the case of multiplication there are further complexities. The digit of the units in the multiplier is consecutively brought in relation to the digits for the units, the tens, etc., of the multiplicand. If one puts every cipher exactly in the right column the result of the computation by figures is a notation representing the product.

It is useful to realize the intricacy of this method of calculation, which took centuries to develop to its present level. By this method one can work with numbers and solve calculations which without this complicated semantic system would have been impossible.

The sources of difficulty within this method are manifold, as are the procedures which must be learned. For some children, the difficulties, especially of subtraction and division, prove unsurmountable. Without constant training many tricks (especially of division) are forgotten soon after the school years.

Obviously there are many sources of failure in calculation in the case of mental disturbance due to cortical lesions. However, these failures always bear the stamp of *our* method of calculation and of *our* notation system, that is of the difficulties and intricacies inherent to this peculiar system. No doubt there still existed other difficulties and disorders in the case of finger calculation, the use of the abacus, or with Roman numerals, and probably even greater when one thinks of such a problem as CLXXIV × XCVII.

The disturbances we can deduce theoretically from the semantics of calculation are repeatedly seen in patients with acalculia. Unawareness of the necessity to rearrange the groups; inability to arrange units, etc., in columns; failure to bring the digits of one number in relation with the corresponding digits of others in an addition or with all the figures of the multiplicand in a multiplication, are frequent errors with such patients.

The procedures of "carrying over" and "borrowing" may be forgotten; or the patient may no longer remember how to proceed. He may write down the 1 of 15 in the wrong place, e.g. under the 5 or in the column of the tens. He may have a vague memory of what he is expected to do but be at a loss to realize it. Horizontal and perpendicular directions may be confused; the fact that 12 × 17 is identical with $\begin{smallmatrix}17\\12\\\hline\times\end{smallmatrix}$ may prove bewildering.

In short, the numerous failures in calculation which these patients show are understandable as soon as we start from the semantic system of number-notation and the ensuing semantic (or better syntactic) system of calculation—calculation being taken as computation by means of our system of figures.

Following Berger (1926), we distinguish between primary and secondary acalculia. Many mental affections such as dementia, memory and retention disorders, perseveration and aphasia, may cause difficulties in calculation. The partial sum or product may be forgotten before it can be utilized, e.g. in mental arithmetic. The tables may be lost. Or there may be a disturbing perseveration of a cipher, e.g. $7\times7=47$, or $9+13=13$; or of a sum, e.g. $6+6=12$, $6+8=12$, etc. Inability to formulate the answer because of aphasia may prevent its notation.

Cipher agnosia and apraxia generally result in acalculia. A visual factor plays a part in calculation; but it has been shown experimentally that there is no parallelism, even no manifest relation between mental arithmetic and visualization or "Gestalting" ability; nor between ability in calculation and visual or acoustic powers.

In cases of primary acalculia, calculation itself is affected; though on deeper analysis one finds that calculation is a complicated psychological procedure that may be disturbed or hampered in many ways. As a rule mental arithmetic suffers more than calculation on paper.

Henschen (1926) already stressed the fact that every calculation, even the most simple one, is a mental process, and one which confronts us with a problem requiring a series of thinking tasks. Ranschburg showed experimentally with well-taught children of the higher classes in a primary school that even simple sums always demand a certain effort. Berger (1926) thought that disturbances of logical thinking are always accompanied by acalculia; this is not true, though arithmetic does presuppose a more or less intact intelligence.

The occipital type of primary acalculia is the result of gross lesions of that part of the brain. It can be explained only in part by difficulties in the handling of cipher symbols and by impaired visual retention and visualization.

Cases of frontal acalculia are said to show more severe disturbances in

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dealing with abstract than with concrete numbers. My experience does not confirm this assertion. Though psychologically the concrete precedes the abstract, the latter being based on the former, in patients with acalculia there is a deterioration in computation and there is no reason why this should be expressed more in abstract computation. Moreover, while addition and subtraction may in the first instance be limited to numerical quantities, multiplication and division necessarily introduce the idea of pure number. Practical calculation on the other hand makes use of a well-learned conventional technique, and at any rate in a multiplication only one of the numbers can be concrete. Finally it remains an open question whether any number is ever really abstract. We may conclude from these remarks that the idea of abstract and concrete numbers in frontal acalculia is superficial. The intensity of acalculia in frontal lesions shows a certain parallelism with the general lowering of the level of productive thinking and of initiative in these cases.

Hitherto, from a psychological point of view, parietal acalculia formed the most interesting type of primary acalculia. Henschen (1919, 1920) and Peritz (1918) already emphasized that in lesions of part of the left angular gyrus typical acalculia might ensue. It is well known that small lesions in and around this area may cause several symptoms: disorders in thinking and in language, disturbances of left-right orientation and of the body scheme. In Gerstmann's syndrome, finger-agnosia, acalculia and sometimes agraphia—another symptom of this region—are combined.

Such patients often show that type of apraxia described by Kleist (1936) and his pupil Strauss as "constructive apraxia." It is a disorder of spatial handling and modelling, though there is neither paralysis nor apraxia, and the awareness and the planning of the task to be fulfilled is unimpaired. This disturbance can best be demonstrated by drawing, and in constructions with blocks or sticks. One realizes that these patients are incapable of forming spatial relations though well aware of this defect.

Krapf (1937) showed that such patients often cannot write down a plural cipher notation. In written sums they cannot combine ciphers and numbers correctly: horizontal and perpendicular directions are interchanged. The same occurs in drawing. According to Krapf, the fundamental disturbance in these cases of parietal acalculia is an inability to manipulate spatially parts of number notations and the parts of numbers (notations) in relation to each other. One might perhaps call this "constructive acalculia." Few cases of acalculia have been adequately studied along these lines; in my own cases the picture was always much more complicated.

Several problems remain. For example, why does counting become more difficult beyond the figure 10; why is one operation still possible

while another, apparently an easier one, is not? From a psychological standpoint there are often paradoxical features in these cases, as, for example, when a patient cannot subtract 9−6, but nevertheless gives the unexpected answer to 9+6 as 3. Or a patient may not be able to add 1+8+3, but afterwards asked to make a number containing a 1, 8 and 3 he answers 12. It has been said that automatization and spontaneity have suffered in these cases or that tasks are carried out passively which they cannot solve actively. Singer and Low (1933) remarked that this is a translation rather than an explanation. In my opinion the cause of this phenomenon lies in an impairment of the so-called "distributive attention," as seen in frontal and parietal lesions.

The rare and laborious follow-up studies of cases of progressive acalculia give a deeper understanding of the psychology of acalculia, provided that one looks upon calculation as a highly complicated symbolic-semantic system and upon its disturbances as a series of highly diverse disturbances of the manipulation of this system. With this in view, one notices that in various types and grades of acalculia different faculties and different parts of the procedure of calculation have suffered. In the most severe defects the notion of aggregate and/or of quantity may have been lost, or the insight into the conception of part and whole has disappeared. The relation of bigger and smaller may have lost its meaning, though seldom if ever is it found that a patient who still has a vague idea of what subtraction means, will try to subtract the bigger number from the smaller one.

Counting may be impossible. The unambiguous correspondence between a number, viz. a numerical quantity, and the manifold it represents may no longer be clear to the patient. The so-called transitive rule in arithmetic may no longer be evident. These are all intellectual and ideational disturbances.

Moreover a patient may show asymbolia not only for the ciphers but also for the operational symbols (+, −, =, etc.), that is for the whole of the so-called pasigraphic system. In these cases the relation between the language symbols of numerical quantity, that is the name of the numbers, and the ideographic notation system of ciphers and signs used in number and calculation notation, is disturbed. In this connexion it is necessary to point to the remarkable fact that for the notation of ciphers, numbers and operational symbols we make use of an international ideographic system, not only independent of the system of language notation, but also of linguistic formulation. Thus "3" is "three," "trois," "drei," "tre," "drie," and so on; 3 is the symbol for the idea three, or for the fact ///, or for the numerical quantity three; 3 is a notation symbol; but 3 is *not* a rendering or reproduction of the *word* three. This fact explains that

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asymbolia and agraphia for letters and words and those for ciphers and numbers do not always concur; the one and the other represent different systems of symbolization or different semantic systems. In parentheses we may add that the semantic system used in musical notation is independent of the others and therefore each of the three systems may be affected independently of the other two. Often each one is impaired, but with very different degrees of intensity.

Since the various disturbances of computation, calculation and of notation, as well as the constructivo-apraxic defects, often go together, sometimes being combined with language disorders and dementia, it will be obvious that the study of acalculia offers many difficulties.

One point to be remembered is the fact that our language denomination of numbers generally follows a certain rule; e.g. 3456 is three thousand, four hundred, fifty, six. But this parallelism does not obtain in every case. In many languages the denomination of the teens follows another rule of succession; e.g. 14 is four-teen and not ten, four. This divergency exists in different languages for different numbers; it therefore is a source of different agnosic-apraxic troubles in these languages according to their linguistic peculiarities.

It is not our intention to go further into the special problems of the different types of acalculia. One example may suffice to show that the study of acalculia may afford a deeper psychological insight into the problems of arithmetic itself. It has been maintained that arithmetic must be looked upon, and therefore studied and taught, from a Gestaltist point of view. One of Wertheimer's (1912) earliest studies dealt with calculation in primitive peoples from the Gestaltist angle; in his opinion a holistic approach to the problems of arithmetic was necessary. Fettweis (1927) was able to show that in reality primitive peoples usually have some notion of number.

In our experience cases where the conception of aggregate, of quantity *per se*, has suffered, are very rare. Most patients with acalculia have retained the notions of whole and part, of bigger and smaller; but they still cannot calculate. In the first mentioned rare cases, Wertheimer's Gestalt considerations have their value. However, in most cases of acalculia as our analysis has shown, it is not the configuration of groups, but the command over the symbolic-semantic system which has suffered; this aspect of calculation is relevant in the disorder. This is the place to point out that the regrouping in computation, e.g. $8 + 7 = 10 + 5$ is not a regrouping of Gestalts but the manipulation of counted elements, viz.:

$8 + 7 = 8 + (2 + 5) = (8 + 2) + 5 = 10 + 5$; or

1, 2, 3, 4, 5, 6, 7, 8, ...

. . . . . 1, 2, 3, 4, 5, 6, 7,

1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15.

The Gestaltist point of view does not hold good in the study of modern arithmetic and its advocates (e.g. in the school) get no support from the study of acalculia.

As already shown, a differentiation between asymbolic and asemantic acalculia is fruitful.

The asemantic types of acalculia remind us of Head's (1926) semantic aphasia. In these cases the patients do not grasp and do not realize the full implication, the wider meaning of what has been said. These patients moreover no longer understand games, cards or caricatures. If one refers to the case-histories in Volume II of Head's book one finds that every one of these patients showed a manifest acalculia. Moreover, all of them had outspoken constructional disturbances. It is well known that Head localized their cortical lesions to the supramarginal and angular convolutions, but it is often forgotten that Head described these symptoms even before Kleist and Straus.

The fundamenttal common factor of many of these disturbances is an asemasia, revealing itself in different semantic systems.

Certain considerations require discussion: In the first place arithmetic appears to be such a complicated process that a simple cortical (and functional) "localization" is out of question. Its study confronts us with the rapidly developing branch of neurology, namely, neurological psychology or neuropsychology. This study requires an adequate knowledge of modern psychology and our study may demonstrate that when we are dealing with "new" problems semantic analysis of the functions studied is necessary as well.

Secondly, we realize that with the study of aphasia, agraphia, and acalculia, a special domain is opened to neurology. In these syndromes it is not a biological function which has deteriorated, as in the case of a hemiparesis, but it is the patient's participation in cultural acquisitions, in acquired cultural patterns which is disturbed, viz. his sharing of a language system, of a graphic notation system, of a calculation system. This offers an opportunity for a more intimate co-operation between neurology, social psychology and cultural anthropology.

Thirdly, the result of our analysis sets us speculating about the possible intimate relations between our mental make-up and our bodily constitution. The combination of finger-agnosia with acalculia is all the more remarkable, because our counting probably had its origin in pointing (that, and that, and that) or/and in counting on the fingers. The use of the denary scale in notation is due to its use in numeration and this again springs from the primitive use of the fingers for counting, as exemplified

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in English by the use of the word "digit." Is not acalculia then an unavoidable accompaniment of the loss of the knowledge of one's fingers?

Further speculation is tempting. Considering acalculia in its relation to difficulties with spatial manipulation, i.e. with the control of one's space (body and action space, or near and distant space), and even with the concept of time (as was the case in Head's patients), one may attach a great value to Descartes' happy idea of attaching numerical value to vectors. Herewith analytical geometry was founded, geometry came within the scope of measure and number, and algebraic formulas could be depicted. This means that counting and the scheme of three-dimensional space were brought into intimate relation. Is it not then remarkable to see that anatomical lesions causing disorders of calculation are so often accompanied by impairment in the control or command over space? Can it be then that anatomical proximity within one convolution is the real basis of Descartes' intellectual combination?

One must beware of the lure of such speculations. We know that acalculia, agraphia and many subtle disturbances are seen with lesions of the parieto-temporo-occipital borderland, but that spatial disturbances, in part at any rate, are due to gross subcortical interruption of pathways correlating the "praxis" of the hand with the visual field, i.e. with the "guiding eye." On the other hand the three-dimensional space of geometry is not our "real" biological space, but merely a useful schema; and as such it is itself part of yet another semantic system. We are not permitted to use these schemata as if they were realities, so committing what Whitehead has called the "fallacy of misplaced concreteness." This means that Man's creative thinking permits him to lay connexions between a certain space scheme and his arithmetical system, but that there is not the least "real" connexion between both. Man's specifically human analytic-synthetic power (i.e. Spearman's "correlative" power): his ability to create as it were connexions, relations and correlations; his gift to fix these relations in symbols and his faculty to handle them abstractly lie at the foundation of the correlating of different schemes such as Descartes did.

Many of the psychological disturbances treated in this study may be explained by a shortage of these faculties of relating, correlating, and symbolizing, as well as of the semantic faculty. When these highest intellectual faculties of Man are impaired we are confronted, amongst other things, with asymbolic and asemantic disturbances.

This insight is a more realistic basis for science than speculations and æsthetic pseudo-scientific pursuits. As for the new field of neuropsychology, illustrated in this article by the example of acalculia, it must be founded on a sound combination of neurological and psychological exact research.

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A PECULIAR FORM OF PERIPHERAL NEUROPATHY

Familiar Atypical Generalized Amyloidosis with Special Involvement of the Peripheral Nerves

BY

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I.—Introduction

About the end of 1939, we were struck by a case we observed for the first time in the out-patients department of the Santo António Hospital in Oporto. It was that of a woman, 37 years of age, who had been living for seventeen years in Povoa de Varzim, a fishing town in the Oporto region. The patient's neurological syndrome, history and clinical picture, made us think we had before us a clinical entity as yet unknown, and therefore worthy of particular attention on our part.

Our first impression was strengthened by the fact that we were aware a condition existed in Povoa de Varzim, known in the area as "Mal dos pèsinhos" ("Foot disease"). This is an endemic disease with the following characteristics:

(1) Paresis in the extremities, particularly the lower ones.

(2) Early impairment of thermal and painful sensibilities, beginning and also predominating in the lower extremities.

(3) Gastro-intestinal disorders.

(4) Sexual and sphincter disorders.

This disease, beginning insidiously and prevalent in various unrelated families, impressed us by its progressive nature and extremely high rate of mortality. There have been various diagnoses according to the patient's first symptoms and the specialist he consulted. These symptoms might be neurological, gastric, digestive, etc.: hence the illness was labelled syringomyelia, myelitis, tabes, colitis, appendicitis, avitaminosis or leprosy. We learnt from information gathered among the people of the district that the disease had a very long history. Through the years it has taken great toll of lives. We observed some patients in their homes and in the Hospital da Misericordia, in Povoa de Varzim. This enabled us to get an idea of the incidence of the disease and to realize the monotonous and

constant nature of the clinical picture, the large number of cases in certain families and the inexorable course of the disease.

Simultaneous observation of various patients strengthened us in the belief that we were dealing with a problem of interest for the clinician, the pathologist and the public health officer. Two patients were admitted to the neurological department of the Sto. António Hospital and we were thus able to follow the course of the disease to the patient's death and complete the clinical study with histopathological observations. This anatomo-pathological study, together with the bacteriological investigations, the examination for the leprosy bacillus and the examination of biopsies of various organs, revealed certain aspects that were also constant and peculiar to the disease.

Pursuing our studies, we have since observed 74 cases belonging to different families, people of the most varied social classes and with very different dietary habits. Upon consideration of (1) the peculiar anatomical and clinical aspects of the disease; (2) its high mortality rate; (3) the obscurity surrounding its ætiology and pathogenesis and, consequently, the series of problems which arise, we think it opportune to make known this peculiar form of peripheral neuropathy.

II. Clinical Study

The clinical definition of the disease would seem to be as follows: it is a disease that attacks many members of a family but the families in whom it occurs have no genetic relationship. It begins insidiously in the second or third decade of life. Its course is gradual, lasting on an average seven to ten years, with a high mortality rate. Death ensues from cachexia, intercurrent infection or cardiovascular collapse.

It is characterized by the following symptoms: (1) progressive lowering of the general state of health; (2) gastro-intestinal disorders; (3) premature impotence, and (4) a syndrome of involvement of the peripheral neurone starting and predominating in the lower extremities, i.e. impairment of sensibility beginning with thermal and pain sensibilities, paresis and amyotrophy, muscular fibrillation, decrease and abolition of the tendon-jerks, disorders of the sphincters, trophic lesions, atrophy of the epidermis and ulcerations.

(A) *Onset*

Usually the onset of the disease is insidious, rarely sudden. Sometimes the clinical picture appears with all its characteristics at the same time, but in varying degrees of intensity. In other instances the disease is revealed by a single symptom and other disorders appear only after some months.

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(B) *Analysis of Symptoms*

Disturbances of sensibility can be divided into two categories, (1) Hypo- or analgesia, or (2) Paræsthesiæ.

Patients may not realize the existence of pain or thermal anæsthesia until an accident, an injury or a burn, usually in the foot, reveals it and the patient is alarmed, thinking he has unconsciously burnt or injured himself.

The paræsthesiæ include tingling, pricking, shooting pains, pinchings, "pins and needles," etc., of variable occurrence and localization.

In some patients these paræsthesiæ may extend over a larger area, involving the whole body from the outset, and later being localized in the feet and legs. In one case the patient's scalp and cheek were also involved.

Patients complain of diffuse pains in the muscles of the legs and feet, and some compare them to aches resulting from long walks. In one case this symptom, together with a lowering of sexual potency, was the only disturbance noted for months. Another symptom observed was tingling of the skin. Contact with clothes or the slightest friction caused the patient a most unpleasant sensation, a mixture of burning and pain.

Another rather interesting phenomenon has been noted. Cutaneous stimuli, even slight ones such as the repeated contact with cotton or gentle surface-scratching, caused referred pain. In one case, stimulating the external surface of the lower third of the leg caused pains in the toes.

From an objective examination of sensation we conclude that the first mode to be affected is thermal sensibility, followed chronologically by those of pain and touch and, finally, by postural loss. As a rule the impairment begins in the extremity of the big toe and if we observe attentively, stimulating small areas, we find that little areas of anæsthesia alternate with others where the sensibility is unaffected. Vibratory sensibility is irregularly affected in contrast with what is observed in other forms of peripheral neuropathy.

We have observed cases of dissociation in which either cold anæsthesia or heat anæsthesia predominated. Thermal anæsthesia is almost always preceded by delay in perception, rapid extinction or perversion of sensation. As the process goes on, the areas of disturbed sensibility increase and merge and the anæsthesia becomes more accentuated. In the lower extremity the thermal anæsthesia is then complete and towards the base of the limb we find the same type of disturbance that we had previously observed in the distal end.

In turn the pain, touch and deep sensibility is affected and in advanced stages of the disease we find the following pattern of disturbances going

from the distal to the proximal end of the limbs, (1) an area of complete anæsthesia, (2) an area of thermal and pain anæsthesia and slight tactile hypoæsthesia, (3) a zone of "spots" in which various disturbances of thermal sensibility may be observed.

Motility and muscular state.—Motility is usually affected much later than sensibility. In some cases, however, there are complaints of excessive fatigue accompanied by pains in the deep muscles of the leg. On careful examination of these patients, we were often able to observe slight paresis of the big toe extensor and in some cases we observed the patient's inability to walk on his heels with his feet in dorsiflexion, whereas walking on tip-toe was possible. This reveals the start of paresis in the extensor muscles of the foot.

The decrease in strength does not always develop parallel with muscular atrophy and the state of the muscles when examined by palpation and passive extension is very variable. In some cases, total loss of muscular volume and consistence is observed in association with general wasting (disappearance of all subcutaneous tissues. In other patients the trophic state of the muscle seems at first fairly good but inspection reveals fibrillation.

The examination of idiomuscular contraction also provides us with useful information: namely, absence of contraction, slow contraction or contraction of a myotonic character. In 2 patients we observed a rather interesting fact; when we were using the passivity test, we noted that after the "ballotment" of the feet (André Thomas test) the anterior tibial muscles and the toe extensors contracted slowly a few moments afterwards and the contraction lasted some time. The same phenomenon was observed when we provoked the myotatic reflex. The electrical examination of one of the patients showed reactions of myotonic character. This fact raises the question of the possible co-existence in some patients of primitive muscular lesions associated with those of neuropathic origin.

The association of disturbances in sensibility with those of motility of the lower limbs give a peculiar "steppage" character to the gait. In Povoa de Varzim it is not unusual to see fishermen, once robust and full of vitality and now thin, weary and resigned-looking, walking slowly and bending their knees excessively to compensate for their foot-drop.

Reflexes.—In the initial stage of the disease the tendon-jerks are frequently present, but in more advanced stages the ankle-jerk and the knee-jerk are lost. In the final stages the jerks of the upper limbs also disappear. We have, however, noted that in some cases the tendon-jerks disappear at the beginning of the disease.

Sweating.—We applied the pilocarpine test in 2 cases and observed

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coincidence of the area of anidrosis and the areas of the thermal and pain anæsthesia.

Trophic lesions.—In some cases perforating foot ulcers are present. Their characteristics differ in no way from the trophic ulcers seen in other conditions. They have the same distribution as the disturbances of sensibility but we cannot be sure whether there is any connexion between the frequency of the ulcerations and the severity of the sensory disturbances. They almost always heal up when properly treated and they may be painful or painless. We have never found in the products of scratching of the ulcer or round its edges any acid-resisting bacilli, in particular the leprosy bacillus. Besides the ulcers, atrophy of the epidermis and hyperkeratosis may be found.

Pupils.—In many patients we observed anizocoria and the weakening of pupillary reactions to light and convergence. In two patients we noted a particular appearance. The pupils had irregular outlines and fringed edges (*see* fig. 1) and were different in size. In the left reflexes to light

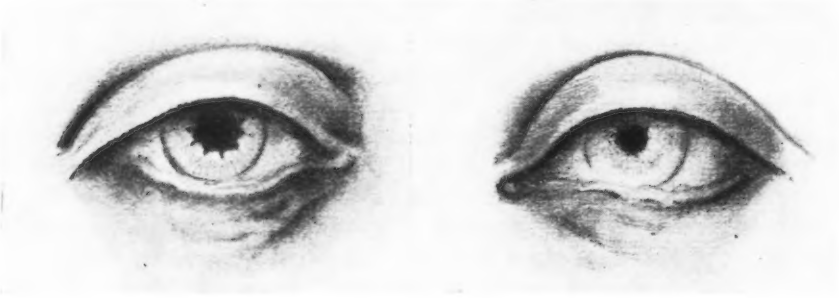

FIG. 1.

(direct or consensual) still existed but were weak. In the right the light and convergence reflexes were lost. Atropine brought about complete dilatation both on the left and the right while reactions to myotics (eserine and pilocarpine) were completely abolished.

Gastro-intestinal disturbances may be of any kind, from slow digestion with the sensation of a distended stomach, persisting and severe constipation, occurring long before the other symptoms, to severe and prolonged diarrhœa, which, when accompanied by disturbances of the sphincters, may be very distressing for the patient. In 2 cases the acute gastro-intestinal syndrome is referred to as marking the beginning of the sufferings.

A fisherman patient (Case I) told us how he had fallen into the sea when at work one day. He had swallowed a lot of sea water and had had difficulty in saving himself. After his accident he had gastro-intestinal troubles, with vomiting, profuse diarrhœa and violent colic. From that day on he was never free from his digestive sufferings and in a few months' time he began to feel paræsthesiæ in his feet and he lost sexual potency. From time to time against an ill-defined background of gastro-intestinal symptoms, which may take the patient even to the operating table, the sudden onset of intense sickness and diarrhœa, accompanied or not by intestinal colic, stands out sharply. This brings about a considerable lowering of the general state of health and (possibly through concomitant secondary avitaminosis) the aggravation of the neurological symptoms. If the diarrhœa continues there are signs of avitaminosis (atrophic red tongue, anæmia, saw-edged teeth).

Loss of weight and asthenia are not always accompanied by lack of appetite and digestive disturbances. Often, there is gradual, inexplicable loss of weight in spite of good appetite and an apparently well-balanced diet. This loss of weight is constant and progressive in all cases, and it seems to indicate a profound disturbance in nutrition and metabolism. We have not observed any constant chronological relation between the neurological and the digestive troubles.

Sexual disturbances are one of the most constant and earliest symptoms in our patients' histories. In a 22-year-old young man, without any previous psychoneurotic history and with a full normal sexual life, the lowering of potency appeared as the only symptom, accompanied by a secondary—and understandable—psychogenic reaction; for this reason he was treated as a case of psychical impotence. His clinical study was completed by biopsies of the testes, of the gastrocnemius and determination of the 17-ketosteroids and gonadotropins in the urine. The result of these examinations was very instructive. We found atrophy in the seminiferous tubules with azoospermia, spermatogenesis being arrested at the spermatid stage, muscular atrophy and lowering of the values of the 17-ketosteroids and gonadotropins. At the present moment genetic and gastro-intestinal troubles and loss of weight still predominate in this case. Disturbances in sensibility and motility are still very slight; the tendon-jerks are only now getting weaker.

In the initial stage impotence is not always accompanied by azoospermia or lessening of libido. But in the end the process is complete. The orgasm may be preserved and erection completely abolished.

In no case did we find any change in secondary sexual characteristics, in particular falling of hair and gynæcomastia.

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Laboratory findings.—Laboratory investigations were carried out in order to verify the various diagnostic hypotheses as they arose. At first we insisted upon investigations for Hansen's bacillus (in nasal mucosa, skin scrapings and in all histological sections observed) and for hydrochloric acid in the gastric juice, as well as on hæmatological data, Schmidt tests and examination of urine. In 8 cases we performed lumbar punctures. More recently we have also studied the 17-ketosteroids, gonadotropins and blood proteins. The Benhold test was also applied. Of all these tests, the only results that for the present seem to merit attention are the following: (1) hyperalbuminosis was found in the cerebrospinal fluid in 6 cases, and in urine in 3 cases; (2) an important lowering in some of the values of 17-ketosteroids and gonadotropins was seen in some cases; (3) Benhold's (Congo-red) test was positive in 3 cases.

To elucidate the clinical study we must add the negative facts to the positive ones, namely that in none of our cases have we observed hypertrophied lymph glands or nerves, cutaneous lesions other than those described, such as atrophy of the face muscles, cataract, iridocyclitis or macroglossia.

III. Histopathological Examinations

The histopathological examinations were made from material collected from two autopsies complete except for the tongue, internal secretory glands other than the pancreas and the bone-marrow, the nerves at all points being examined in great detail; in a third case it was only possible to examine the sciatic, common peroneal and internal popliteal nerves, the testes and some muscles. Three biopsies of the testes and one of the gingival mucosa, one of the skin and various biopsies of the muscles were also made.

We may summarize our findings as follows: the most important histological alteration consists of the presence in large quantities of a hyaline substance that by the use of special staining methods was identified as amyloid, that is to say, the histological study showed that we were dealing

	Case I	*Case II*
Aorta	++	Not studied
Heart	+++	++
Intestine	+	Not studied
Kidney	++++++	++++++
Liver	+	+
Lungs	++	Not studied
Pancreas	++++	++++
Peripheral nerves	++++++	++++++
Skin	+++	+++
Spleen	++	+++
Stomach	+++	+++
Striated muscles	+	−

with generalized amyloidosis; the distribution and predominance of these amyloid deposits in organs and tissues ordinarily unaffected in secondary, classic amyloidosis, enable us to classify the condition with Lubarsch's atypical amyloidosis ("paramyloidosis" according to other writers).

The table on p. 414, summarizing the findings from the two autopsies, gives an idea of the distribution of the amyloid in the various organs.

These results are entirely in agreement with those found by Wohlwill in a case examined and published by him in 1942.

As can be seen from the table, as in typical generalized amyloidosis, the kidney is always severely affected. This organ was not examined in Wohlwill's case; in our cases amyloid is deposited in the glomeruli, in the walls of the vessels, in the basement membranes of Bowman's capsules and tubules and in the interstitial tissue. The densest deposits are found in the outer part of Malpighi's pyramids. In both cases there is a considerable nephrotic element.

Contrary to what happens in secondary amyloidosis, the liver and the spleen are only slightly affected here. In the spleen the deposits form in the vessels, the septa and the capsule, never in the follicles or the pulp; in the liver only some vessels in Kiernan's spaces show amyloid.

After the peripheral nerves and the kidney, the pancreas is the organ most severely attacked by the disease. Amyloid substance is here found in practically all the vessels, the nerve, the walls of the excretory ducts, the interstitial tissue and even within the lobes. As a consequence of these abnormal deposits a considerable part of the parenchyma of the organ is destroyed. It is not easy to say to what extent the diarrhœa observed in our patients can be attributed to these lesions of the secretory part of the gland, in themselves or in association with amyloidosis of the nerves of the organ and the sympathetic nervous system in general.

Considerable deposits of amyloid substance are also found in the connective tissue of the stomach (connective tissue of the muscularis mucosæ and the muscularis propria), the aorta and the skin (erector pili muscles). Amyloid deposits are found in connective tissue of the testes as well as in the vessels. Although the interstitial gland seems to suffer very little, spermatogenesis may be considerably affected.

The lesions in the peripheral nerves deserve special mention. As in other organs, the histological aspect is dominated by the presence of amyloid but the alterations in the parenchyma are of exceptional importance.

In slides stained by the Kulschitsky method we find a severe destructive process in the myelin sheaths, a process that is particularly severe in the nerves of the lower extremities. This degeneration of the myelin is accom-

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panied, though much later, by destruction of the axis cylinders and proliferation of the Schwann cells.

The examination of a large number of slides enabled us to reconstruct the evolution of the process and to analyse some of its characteristics. At an early stage the most striking alteration is the extraordinary affinity displayed by the sheaths for ammoniacal silver; whole sheaths with their neurokeratin network are as clearly stained by the Bielschowsky method as in the specific colorations for myelin. Atrophy of the fibre follows. This consists essentially of a progressive reduction in volume and a decrease in affinity for hæmatoxylin. Usually there is no break in the continuity of the fibre and there are very few myelin ovoids. As the fibre gets paler and more slender it loses its affinity to silver, the neurokeratin network becoming invisible. The destruction of the myelin is not accompanied or followed by the presence of myelophages and no compound granular corpuscles are found. In none of our slides did we find phagocytosis of the myelin sheath and the stainings for neutral fats constantly gave negative results; nor did we ever see inflammatory reactions.

The deposit of amyloid usually accompanies the degeneration of the nerve fibres. These deposits are formed either within the nerve bundles, separating the nerve fibres whether in the endoneurium, perineurium or vessels. In most cases it takes the form of rounded masses with more or less regular outlines but it may appear in the form of striæ or irregular deposits. These various deposits show extreme affinity to silver and stain here, as in the remaining organs, by Congo-red, methyl violet and Lugol. These lesions are not essentially different from those observed in the roots and spinal ganglia. Amyloid is deposited in the latter on the connective tissue or it infiltrates the parenchyma, involving the nerve cells.

The examination of the spinal cord enabled us to eliminate with certainty the diagnosis of syringomyelia. Only a slight degeneration of the posterior columns and a retrograde type of degeneration of the anterior horn cells were observed. Finally, we may add that although atrophy of the striated muscles seems to be of neuropathic type, we cannot eliminate the possibility of the coexistence, at least in certain cases, of lesions of primary atrophic character.

IV. Case Reports

From 1939 to 1948 we observed 64 patients and since then we have seen 10 further cases. We have regularly followed up the progress of many of these patients.

In the first table the patients are classified according to their professions or occupations. The familial or isolated nature of the cases is shown as

TABLE I.—PATIENTS OBSERVED (1941–1948)
Total 64

Professions

Housewives	19
Fishermen	12
Rural workers	11
Tradesmen	4
Doctors	2
Carpenters	2
Judge, Engineer, Soldier, Tinker, Plasterer, Bathing attendant, Tram driver, Dressmaker, Electrician, Watchmaker, Jeweller, Day labourer, Domestic servant, Shoemaker each	1

Genetical influence

Cases: Familiar 51 — Genetically independent 10; Related genetically 2 } 12 families
Cases: Isolated 13

Sex

♂ 42
♀ 22

Evolution

Death 17
Duration 7–10 years

well as the duration of the disease. We have studied the genealogical trees of 12 families where the disease has been known for a very long time. In 2 families we were able to examine patients of two generations. We constructed the trees of other families, basing them on the patients of the generation observed and the description of clinical pictures made by doctors and members of these families. As the clinical picture observed in our 74 cases is always the same and very characteristic and as we have observed it in 12 families, we believe that these genealogical trees may provide a useful basis for studying the problem from the genetic standpoint. The second table illustrates the geographical distribution of the

TABLE II.—GEOGRAPHICAL DISTRIBUTION

Póvoa de Varzim	54 cases	Porto	3	10 cases
Vila do Conde		Coimbra	1	
Touguinhó		Braga	1	
Aguçadoira		Aveiro	1	
Rates		Vila Real	1	
Fão		Cima	1	
Esposende		Setúbal	1	
Árvore		Dafundo	1	
Apúlia				
Gandra				
Barcelos				
Laundos				

disease and its prevalence in the neighbourhood of Povoa de Varzim (Oporto district).

Among the cases observed we have chosen I (A. L.) as a complete post-mortem examination was made and II (C. D. P.) as it was the first case in which we made the clinical diagnosis of the disease during the patient's lifetime and were able to confirm the diagnosis with a biopsy of the skin. Recently, the diagnosis of another case has been confirmed by a gingival biopsy.

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CASES

Case I.—A. L., aged 36, single, a fisherman, resident in Matozinhos, a native of Povoa de Varzim, admitted to the Neurological Department, Santo António Hospital, Oporto, June 3, 1941.

History.—He was examined four times between June 1941 and April 1943 and died on May 28, 1943. Post-mortem examination.

In 1936 he accidentally fell into the sea when fishing and had to swim about forty-five minutes to save himself. The effort left him exhausted and he felt slightly dazed when he reached the shore but he was able to walk home after about half an hour. That night he had severe pain in the right hypochondrium, spreading to the epigastrium, continuous and accompanied by vomiting. From then on he suffered for weeks from constipation, vomiting and violent colic. Working for a long stretch or taking food brought on the same pain in the hypochondrium. It was so severe that he had to lie down for a quarter of an hour or more with his knees up. If he ate anything he felt the colic returning after a few moments. His diet consisted mainly of rice, salted codfish, sardines, cabbages and coffee, but for a year it was very deficient because he vomited almost everything. Two months after the accident he noted a lowering of sexual potency. This process continued until it was complete. In 1937 his digestive troubles took on another aspect with the occurrence of attacks of diarrhœa which thereafter never left him. It was a liquid, greenish-yellow diarrhœa which almost always followed meals and was usually preceded by colic. At that stage the pains were along the line of the colon, appearing or increasing with meals and ending with an attack of diarrhœa. He felt very weak especially in his lower limbs.

Towards the beginning of 1938 he noticed that his feet were insensitive to pain when he did not feel a nail which got stuck in the sole of his left foot. More or less at the same time he began to feel paresthesiæ in the soles of his feet and in his toes. They began in his knees and descended to his toes. When he put his feet in water he did not feel the temperature of it. The wound caused by the nail did not show any signs of healing and it was even suggested that his foot should be amputated. About the middle of 1938 he gave up work owing to lack of strength and, except for slight modifications, his state of health remained the same until he was admitted to hospital. In 1940 he had an attack of jaundice lasting for a fortnight. He had a temperature and more severe pains than usual. The fæces continued to be coloured and the urine very much so. He afterwards returned to his usual state of health and the episode was not repeated.

When admitted to hospital (3.6.41) he complained of (1) gastro-intestinal troubles: diarrhœa, colic, indigestion, and the sensation of a full stomach after meals; (2) loss of sensibility, legs and feet "going to sleep," feet (more especially the left foot) insensitive to heat, cold and pain; paresthesiæ in legs and feet (but rarely in the right foot) and the forearms down to the finger-tips; (3) pains in the knee-joints, ankles and shoulder bones; (4) decrease of strength in the lower limbs, more especially on the left side and in the hands; (5) sphincter disturbances, micturition only possible at times, after an effort and with delay, at other times, involuntary, as, for example, after coughing. He still had the sensation of a full bladder and was conscious of the passing of urine; (6) sexual impotence; (7) well-defined painless ulcers (the size of a florin) on the outer edge of the left foot; (8) asthenia—long walks were a hardship for him; after a time he had to stop and rest a moment; he could still walk about 4½ miles (7–8 km.) however.

Family history.—Father unknown. When the patient was a child, his mother fell ill with disturbances of sensibility in the lower limbs and plantar ulcerations. She died at the age of 36 of this affection. A sister of hers died, aged 35, of pulmonary tuberculosis. The patient lived in Póvoa de Varzim until he was 16.

From then on, after his mother's death, he lived in Matozinhos. His mother's illness lasted six years.

General examination.—General aspect: thin, pale, old-looking, apyretic, mental state normal.

Examination of the skin.—No hairless areas observed. On the right foot there was an ulcer of the size of a florin, with well-defined edges. It was healing.

The subcutaneous cellular tissue of the left leg and foot showed signs of hardening and tumefaction. The skin was dark and parchment-like. The fourth toe of that foot had been amputated at the joint.

Neurological examination.—Cranial nerves: no disturbances.

State of the muscles.—All the muscles are greatly diminished in volume. In the trunk the supra- and infra-spinous fossæ show signs of hollowing out. In the upper limbs early atrophy is observed in the first interosseous muscles, being more pronounced on the right. The circumference of the arms is less than that of the forearms: right arm, 23½ cm.; left arm, 24 cm.; right forearm, 25½ cm.; left forearm, 25 cm. In the lower limbs the inner surface of the left thigh is slightly hollowed out. Circumferences: thighs—right, 36 cm. left, 34½ cm.; leg—right 24½ cm.; left 23 cm.

Active motility.—Lower limbs: when supine he can make movements of all segments with the lower limbs but his capacity for extending his feet, especially the left one, and the big toes is greatly diminished. The foot movements are, moreover, slow and rather feeble. The separation and extension of the toes is incomplete. The strength of the upper limbs is normal. When in a standing position he cannot remain on tip-toe or raise his toes while putting his weight on his heels.

Upper limbs.—Movements of hands: Grip (dynamometer tests) Right 22; Left 20. Forward stretched arms: no drop.

Tendon-jerks	*Right*	*Left*
Biceps	Weak	Weak
Supinator	Very weak	Very weak
Ulnar	Brisk	Brisk
Triceps	Weak	Weak
Carpometacarpal	Very weak	Very weak
Knee	Abolished	Variable
Hamstring	Abolished	Abolished
Ankle	Abolished	Abolished

Plantar reflexes: R. immobile or slight flexion; L. immobile.

Abdominal reflexes abolished. Sensation (cf. fig. 2).

Vestibular examination: Galvanic and Bárány test. Vestibular-ocular response almost absent in both sides.

Examination on 17.3.42 (Out-patients' Department).

Heterochromia of the iris—the left, brownish green in tone, the right, green. Slightly irregular pupils with tendency to miosis, reacting feebly to light. Myokymia in the lower eyelids, more especially the left one. Greater difficulty in walking. Steppage in both legs, slow and uncertain gait, the left leg being more affected. Slight oscillation of the trunk.

Sensibility.—A considerable loss of vibration sense at the left ankle-bone and knee. Frequent mistakes in recognizing the position of left big toe. Ulcers healed.

The third and fourth examinations (5.8.42 and 22.4.43).

These examinations revealed the steady evolution of the disease. General state

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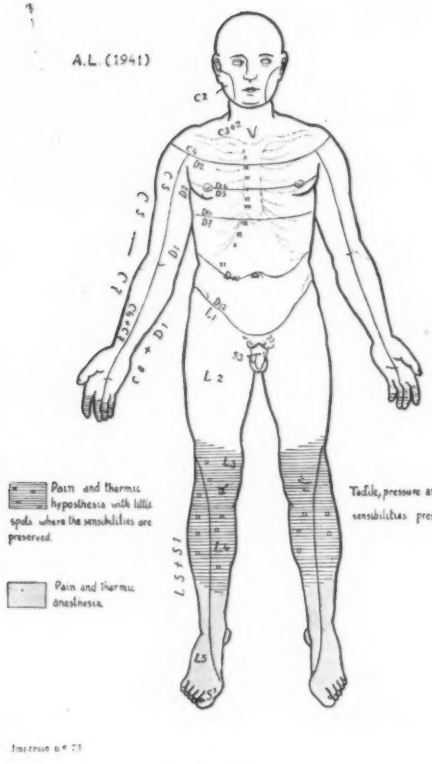
A.L. (1941)
Pain and thermic hypostheseia with little spots where the sensibilities are preserved.
Pain and thermic anesthesia.
Tactile, pressure and deep sensibilities preserved

FIG. 2.

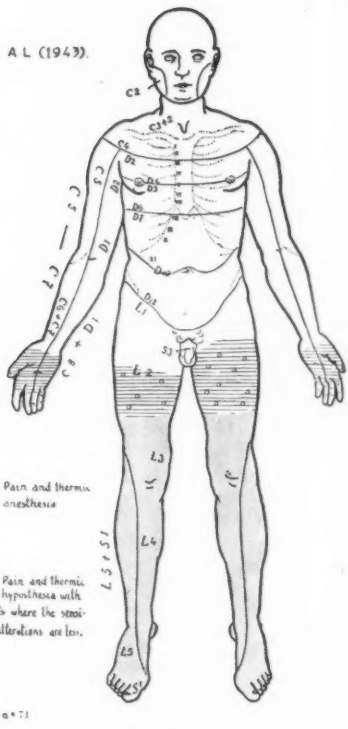
A L (1943).
Pain and thermic anesthesia
Pain and thermic hypostheseia with little spots where the sensibilities alterations are low.

FIG. 3.

worse; increased asthenia; walking more difficult. The gastro-intestinal disorders became progressively worse: the patient suffered from constant diarrhœas, colic, and vomiting. The disturbances of sensibility increased. It was hard for him to distinguish heat and cold in his feet and he could not feel pin-pricks. Motility was further impaired. Finally he had to use sticks to walk and his gait became slower and more uncertain. He could raise himself from a sitting position only with the greatest difficulty. There was a lowering of the general state of health. His blood pressure was 80/35. Axillary temperature: 97·37. He had fainting attacks. He died on 28.5.43.

Hæmatological data 7.8.41.

Hæmoglobin	75%	70%
Red blood cells	3,898,000	3,450,000
Total leucocytes	6,400	7,000
Neutrophils	50%	55%
Eosinophils	3·5%	7%
Lymphocytes	39%	31%
Monocytes	7·5%	6·5%

Wassermann negative. Urea 0·293%.

Urine 17.10.41 and 10.11.41.

Albumin	Normal
Biliary pigments	Normal
Urobilinogen	Normal

Cerebrospinal fluid (9.8.41): Albumin, 0·7 per cent; Cells 1–2; Wassermann negative. Guillain-Laroche test normal.

X-ray: Lungs normal; intestines, signs of chronic colitis; bones of feet, osteoporosis and rarefaction of first phalange of big toe.

Proctoscopy: Relaxation of anal sphincter, two fingers being easily inserted and with a little effort three.

Sigmoidoscopy to 30 cm., normal.

Case II.—C. D. P., a female, aged 35, native and residing in Alpiarça, single, was admitted to Hospital Santa Marta (Faculty of Medicine), Lisbon, 24.5.51.

History of disease.—The first symptoms appeared four to five years ago when the patient began to get thin, perspired excessively and suffered from constipation. Some time later she developed attacks of abdominal colic, sometimes severe, especially when she ate certain foods such as meat, eggs, bananas, stewed or fried food. All the treatments tried proved unsatisfactory and her sufferings increased, diarrhœa alternating with constipation. The diarrhœa was fœtid. Each of these attacks lasted on an average a week and made her very exhausted. She lost her appetite and had a feeling of sickness, with tremors and sweating. She then had a rather long period of constipation lasting almost a month during which she had to resort to enemas. She continued to suffer from attacks of colic that were at times severe. A year and a half after the appearance of the first symptoms (three and a half years ago) she accidentally burnt herself on the foot with a hot-water bottle but did not feel any pain. As a result of the burn a painless blister developed. It became infected and took six months to heal. About the same time there appeared on the plantar surface of the right big toe a small wound that healed very slowly and reappeared later on. Two years ago the same thing happened on the left heel. A year ago the diarrhœa disappeared and persistent constipation remained with less severe colic than formerly. The patient's toe-nails became harder, thicker and more brittle. At a certain stage of the disease, which she could not date precisely, she began to notice burning sensations in her legs and feet, especially when in bed. Latterly she had had these sensations in the lower part of the right thigh. During the last month she has had to make a great effort before beginning micturition and she was always left with the sensation that she has not urinated completely. She never has pain. She was admitted to the Coimbra Hospital but her condition did not improve.

Previous history.—She enjoyed good health until five years ago. She does not know of any nervous diseases in her family nor of any similar ones in the district she lives in.

Examination.—Thin, afebrile, mentally normal. Weight: 41,700 kg.

Muscular state.—In the lower limbs the lower third of both thighs shows wasting, especially the anterior internal part of the right thigh. There is no atrophy of the feet but slight atrophy is noted in the lower third of the legs. The arms and forearms appear to be uniformly thin. The first, third and fourth interossei of the hands are slightly atrophied as also are the thenar eminences, especially that of the right hand. The muscles are flabby to the touch. Occasionally slight transitory fibrillary contractions are noted in the right thenar eminence. Sometimes deep palpation of the muscles or a strong muscular effort causes them to appear but they cannot be elicited by pain or percussion of the muscle itself.

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Extensibility and passive movements are normal in the upper limbs. There is a pronounced and abnormal persistent myotatic reflex which can easily be elicited in tibialis anticus on passive extension of the foot. Afterwards, when the foot is passively plantar flexed, unusual resistance is felt. This increases irregularly and is reminiscent of the cog-wheel phenomenon of Parkinson's disease. Such phenomena are also noted in other muscular groups of the lower limbs but not in the upper limbs. In the lower limbs there is a marked hypotension especially about the ankle and knee. The knee can be raised to touch the thorax and the heel to the buttocks without great difficulty and without causing the patient pain. Dorsiflexion of the foot is limited, however, and attains little more than a right angle. There is slight shortening of the posterior muscles of the leg.

Muscular strength is well preserved in the upper limbs and in the lower limbs there is a relative though not pronounced weakness in the extensors of the right leg and the extensors and flexors of the right thigh.

Tendon-jerks and skin reflexes.—The left ankle-jerk is lost and the right one very weak. The knee-jerks are equal, somewhat brisk and with an increase in the reflex area. All are present in the upper limbs, equal and normal, the supinator-jerk is brisker than the others, however.

Plantar reflex.—Right: stimulation of the outer edge of the foot always brings about a slight abduction and flexion of the fourth and fifth toe exclusively. Stimulating other areas of the plantar surface gives no response.

Left: the response is identical except that the movements of abduction and flexion are slightly less constant and less clearly defined.

State of skin and atrophic disturbances.—There are trophic disturbances on both feet especially in the right toes; the skin here is hypertrophied and resembles a series of layers placed one above the other; dark in colour and with a mother-of-pearl lustre. On the lower inner part of the big toe there is an accumulation of the scaly layers, horny in texture, the size of a flattened finger tip, covering the first perforating ulcer. On the plantar surface of the feet there is wrinkled hyperkeratosis, and a healed perforating ulcer on the right heel with skin similar to that described in the case of the right big toe. The latter is deformed; it is shorter than the left one, partly owing to the irreducible flexion of the second phalange and partly owing to the trophic disturbances of the nail and the perforating ulcer.

In the scapular region and left side of the neck there are small areas of brownish colour. The pigment is irregularly distributed in these areas. It is thicker in some places than others, forming irregular shapes, now little brown spots, now parallel, vertical striations. In these coloured zones there is less hair. The skin is perfectly smooth and does not feel different from healthy skin. It is mobile over the underlying tissues. There are no disturbances of sensibility in these areas.

Sensibility.—(*a*) *Cutaneous* (see diagrams): The transition from areas with sensory disturbances to those of healthy skin is gradual, not abrupt. It has been noted, however, that the transition from analgesic to hypo-algesic area to that of healthy skin is so gradual that it is difficult to say where one begins and the other ends. In the upper limbs there are only slight disturbances in the finger to pain and temperature.

(*b*) *Deep sensibility.*—Vibratory sensibility and stereognosis normal. In the lower limbs the patient makes frequent mistakes in the perception of small movements of the feet and toes.

Laboratory findings.—(1) *Biopsy of skin* revealed *amyloid substance* in the erector muscles of the hairs and the walls of the small vessels.

12.7.51: (2) *Blood*, total proteins 6·3 grains per cent; albumin, 4·5 per cent; globulin, 1·75 grains per cent. Albumin/globulin ratio 2:6.

22.6.51: (3) *Blood.*—Thymol floculation test 2·5 units.

22.6.51: (4) *Blood and urine* Benhold test. Blood: at the end of an hour the blood contains 78 per cent of the original Congo red. *Urine:* after an hour and half urine contains vestiges of Congo red.

28.6.51: (5) *X-rays of lumbar spine* normal. (6) *X-ray of feet,* slight osteoporosis in the first metatarsal and the bones of the big toes. (7) *Chest,* no active lesions. (8) *Stomach and intestines,* reducible colic ptosis. No other obvious signs.

V. Comments

The anatomo-pathological picture we have just described enables us to classify this disease as atypical generalized amyloidosis or paramyloidosis (German nomenclature) or primary amyloidosis (English nomenclature) with special involvement of the peripheral nerves; an entity well defined by Lubarsch from the anatomo-pathological standpoint in 1929. This form of amyloidosis which has been studied in recent years both from the anatomo-pathological and experimental point of view is, however, still rare in world literature since until 1952, according to the bibliographical references we have been able to consult, only about 72 cases have been published. Dahlin in his article on the "Classification and General Aspects of Amyloidosis," 1950, refers to 70 cases of primary systemic amyloidosis and says: "The disease is recognized infrequently." Reports of approximately 70 cases have appeared in literature and in the vast majority, the condition was not diagnosed until the post-mortem examination. Rolv Thingstad also considers primary amyloidosis a relatively rare disease. Krücke in 1950 had found only 50 cases in medical literature.

In 1950 Russel Johns and Donald B. Fraser published an article in which they refer to 15 cases of atypical amyloidosis predominating in the cardiovascular system found among 600 post-mortems. This is the first publication to our knowledge where amyloidosis appears as prevalent in a particular region. The clinical symptoms began almost always in the fifth decade of life or later, and predominated in the cardiovascular apparatus. In some cases reference is made to signs of peripheral neuritis. Yet, if atypical generalized amyloidosis is a rare condition, we may consider as even rarer its occurrence with special involvement of the peripheral nerves. Up to date the cases published are those of Michelson and Linch (1935), Navazquez and Treble (1938), Plenge (1939), Götze and Krücke (1941), Wohlwill (1942), Kernohan and Woltman (1942), Krücke (1942), Maleci and Montanari (1948), Hyman Fisher and Preuss (1951). So that we may still say, as did Wohlwill in 1942, that atypical generalized amyloidosis with special involvement of the peripheral nerves is a rare disease and that the diagnosis of it has been made in the majority of cases by autopsy.

In none of the above-mentioned cases nor in the other forms of atypical

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amyloidosis except in the paper by Ostertag (1949) has the familial nature of the disease been pointed out. This author is the first to refer, as far as we know, to a disease called "familial amyloidoserkrankung" with predominance in the kidneys. In this work he studies the genealogical trees for three generations and calls attention to genetic factors in human pathogenesis.

Besides the observations we have quoted in which the diagnosis was made almost always by an anatomo-pathologist we have found in medical literature a few cases where the history and clinical findings are very similar to if not identical with ours, but in which it is not possible to confirm the diagnosis of amyloidosis in the absence of investigations for in (1) amyloidosis and in (2) of an anatomo-pathological examination.

(1) In 1939 Oswaldo, Freitas Julião, and Couceiro, António, published in the *Revista Brazileira de Leprologia* and in the *Revista de Neurologia e Psychiatria de S. Paulo*, the observations of 2 patients, both Portuguese, one of 34 years, a native of Povoa de Varzim, and another of 29 years, from the Coimbra district, who were sent to the "Centro de Diagnóstico de Lepra." The clinical history and physical examination are very similar to ours, but they do not refer to amyloidosis. The authors describe a primitive degeneration of the nerves with some fatty bodies, unspecific chronic, inflammatory foci and leptomeningitis with adherences to the dura mater in the cervical region. The investigation for Hansen bacillus was negative. The authors say that they were unable to determine the ætiology of the affection, but as a result of the examination, the leprosy ætiology was rejected in both cases.

(2) Alajouanine and Mozziconacci (1940), published a paper entitled "Un cas de syndrome syringomyelique Lombosacré familial cum spina bifida." The clinical picture is in all respects identical with ours except that spina bifida does not exist in our cases. In this communication the authors make a rapid survey of the literature concerning cases similar to theirs and note that up to that date no case diagnosed as familial syringomyelia had been studied anatomically.

Cases similar to the above should perhaps in future be diagnosed in the light of the additional facts we have put forward here.

Differential Diagnosis

If, in fact, the anatomo-pathological picture of atypical amyloidosis is to a certain extent beginning to be recognized and admits of a histopathological diagnosis, the same is not true of the clinical diagnosis. Krücke was, as far as we can judge, the first author who, using the cases of Navasquez and his own, put forward the possibility of building a

clinical diagnosis on the constellation of symptoms. We are of opinion that it is indeed possible to make a clinical diagnosis of this particular form of neuropathy since the clinical picture is very characteristic, in the grouping of the symptoms and in the onset and evolution of the disease. The diagnosis is even easier in cases of a familial nature.

We recognize, however, that in the initial stages the diagnosis may present difficulties. If we consider the various diagnoses that have been made in this country and other places, of patients we have later found to be suffering from this condition, we should, it seems, take into account the following diseases in the differential diagnosis: lumbosacral syringomyelia, heredo-generative diseases, sprue, avitaminosis (beri-beri), and leprosy. All these diseases with the exception of leprosy can easily be eliminated if a history and clinical examination are carefully made. It is more difficult, however, to make a differential diagnosis from nervous leprosy in regions where leprosy is prevalent.

Without any doubt the characteristically neurological symptoms find their explanation in the lesions we have observed: the degeneration of the peripheral nerves. Up to the present it has not been possible for us to study the state of the sensory corpuscles and verify the proportion of degenerated nerve fibres according to their diameter. We think that these observations may be of interest as a contribution to the study of the pathways of sensibility and the problems of pain.

The gastro-intestinal troubles are possibly connected with the lesions in the vegetative system (sympathetic ganglions) or even of the intrinsic nervous system of the gastro-intestinal tract. The negative results of the analyses of gastric juice and fæces together with the digestion tests and radiological examinations and the knowledge that there is a tendency for amyloid to accumulate in ganglia, suggests this interpretation.

Ætiology and pathogenesis.—The problem of the ætiology and pathogenesis of amyloidosis in general and particularly that of generalized atypical amyloidosis present many unknown factors in spite of the research done in recent years in the field of experimental amyloidosis. It is of interest to examine some conclusions drawn by W. E. Heston and Margaret Desinger after their work on the influence of genetic factors in renal amyloidosis in Strain A mice. They conclude that the genetic factor is of fundamental importance for the appearance of amyloidosis. They also showed that certain diets restricted in protein, particularly in protein yielding cystine checked the development of amyloidosis. On the other hand Pisani in the course of his investigations in experimental scurvy on guinea-pigs found that a great percentage of animals that are fed on diets calculated to produce scurvy but do not die of acute scurvy develop generalized amyloidosis.

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These two pieces of work clearly show the indigenous genetic and the exogenous alimentary factors. In the ætiology of these forms of amyloidosis we feel we must emphasize these points since the regional and familiar characteristics also observed in our patients suggest the hypothesis that the convergence of genetic and environmental (particularly alimentary) factors may be the basis for the ætiology of this affection.

In this connexion more careful investigations in the genealogical field and an enquiry into public health conditions, in particular alimentation, would seem to be imperative.

SUMMARY

In this article we present a short account of the anatomo-clinical study of a peculiar form of peripheral neuropathy, characterized histologically by generalized atypical amyloidosis, involving especially the peripheral nerves. The various aspects of the clinical picture are described and attention is drawn to the familial nature of the disease in the majority of cases and its prevalence in certain districts of Portugal.

Though the ætiological and pathogenic factors are as yet unknown, we think that the evidence presented in this study allows us to set apart from the group of the known peripheral neuropathies this entity with its peculiar anatomical and clinical picture.

ACKNOWLEDGMENTS

We are grateful to professor J. da Silva Horta, Professor of Pathology, Faculty of Medicine, Lisbon, for his valuable help in the histopathological examination of the viscera and the identification of the amyloid substance.

We are also indebted to Professor António Flores, for the use of the laboratory of the Neurological Clinic, Faculty of Medicine, Lisbon, Professor Candido Oliveira, for bacteriological examinations, particularly investigations for the Hansen bacillus, Dr. Adelaide Estrada, for hæmatological examinations, Dr. Lobo Antunes, and all the others who have collaborated.

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PLATE VI

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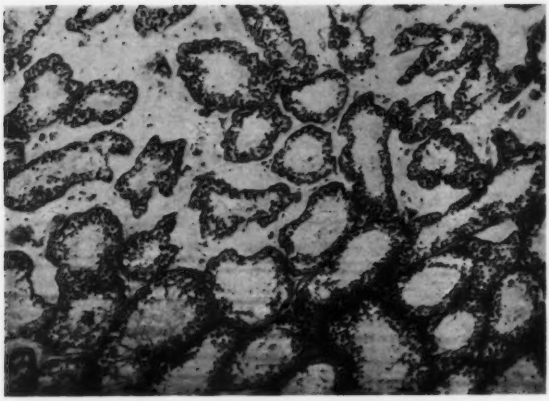

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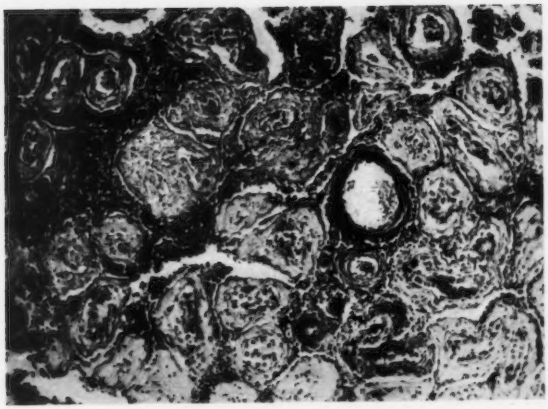

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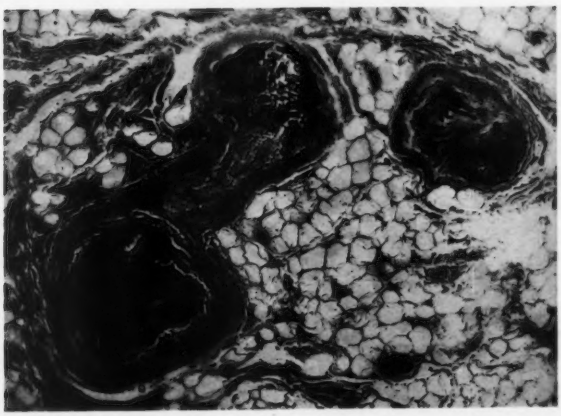

To illustrate article by Corino Andrade.

PLATE VII

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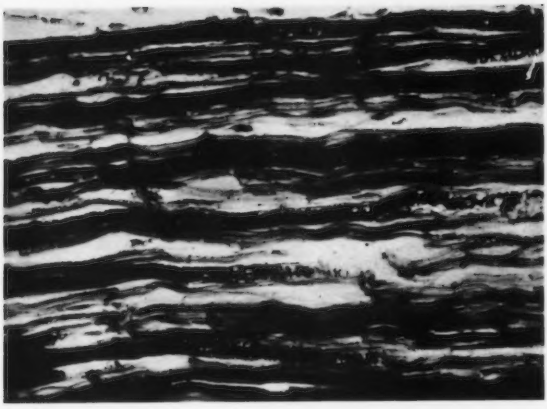

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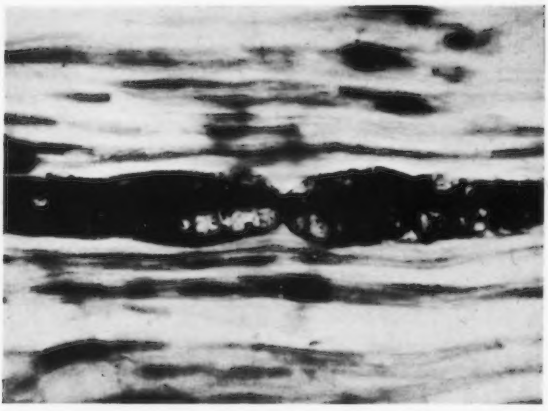

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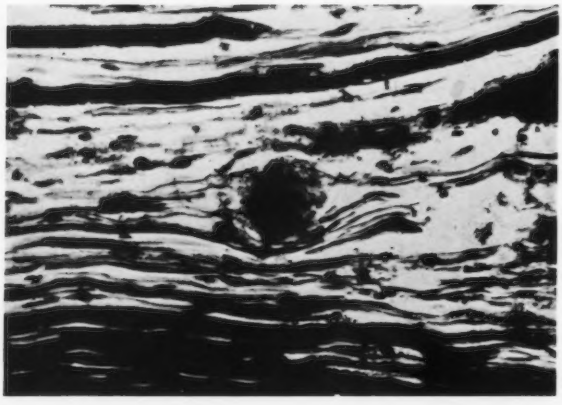

To illustrate article by Corino Andrade.

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PLATE VI

Viscera:

A.—*Testicles*—Atrophy of the seminiferous canals. Biopsy.

B.—*Kidney*—Amyloid infiltration with nephrotic elements. Deposits in the glomeruli, walls of the vessels and interstitial tissue.

C.—*External popliteal sciatic*—Transverse section. Weigert stain—marked myelin degeneration.

PLATE VII

D.—*Sciatic*—Bielschowsky stain. Impregnation of the neurokeratin network by silver. General aspect.

E.—*Detail* (greatly magnified) of this impregnation.

F.—*Detail* (greatly magnified) of amyloid substance of ill-defined structure displacing nervous fibres.

Notices of Recent Publications

Brain Metabolism and Cerebral Disorders. By H. E. Himwich, M.D. 1951. Pp. xii × 452, with 52 figures. Baillière, Tindall & Cox. Price 46s. 6d. net.

Advances in understanding the biochemical processes affecting the body have been outstanding during the last decade or two, and this is perhaps even more true of the brain than of other areas of the body. Metabolic processes in the brain have been widely studied, and the author has done a very real service in reviewing the work so far performed. His book is inspired largely by Hughlings Jackson's theory of the phyletic organization of the central nervous system, and a portrait of him appears as the frontispiece.

The book is divided into two parts, the first on energetics and the second on patterns of nervous activity.

The first part is devoted largely to cerebral metabolism and its carbohydrate supplies, together with detailed descriptions of the fate and uses made of these supplies. The human cerebral circulatory rate and the cerebral metabolic rate are discussed at length. Then follows a chapter on therapeutics and their application to brain metabolism, especially in mental disorders, in which the effects of fever and thyroid therapy on raising the metabolic rate of the brain are discussed. Depressant drugs such as nitrogen, and convulsant drugs such as metrazol are shown to depress the cerebral metabolic rate.

The second part of the book shows the effects of hypoglycæmia and acute anoxia. This is followed by a chapter on the barbiturates and gives full clinical details of their effects, together with various biochemical changes observed, and this whole section is used to demonstrate the truth of Hughlings Jackson's assertions.

The book is well written and contains very few typographical errors. There is a very full bibliography numbering well over 1,000 references, and the author and subject index afford easy reference to any portion of the book. It should prove of considerable value to those interested in cerebral metabolism and to those concerned in mental disorder.

J. N. C.

Epileptic Seizure Patterns—A Study of the Localizing Value of Initial Phenomena in Focal Cortical Seizures. By Wilder Penfield and Kristiansen. Pp. 104. Charles C. Thomas, Springfield, Ill., U.S.A. Price 21s. 6d. net.

This short monograph records work done while Dr. Kristiansen held a research fellowship with Dr. Penfield. It consists of plotting on formal charts of the cortex, the positions of lesions which have been associated with recognized initial epileptic phenomena. There were 222 cases to be analysed and in these the anatomical site has been localized with particular care at operation, in most cases by reproduction of the initial epileptic phenomena, or by recognition of the electrical disturbance in the area of the visibly abnormal cortex. The initial phenomena have been described in the notes, and they were divided into unconsciousness, and motor, sensory, autonomic, and psychical changes. These were subdivided as seemed reasonable

from the subject's description. They were then related to the site of the recognized lesion.

The results were plotted on 15 drawings of the convexity of an average hemisphere and one of its occipital aspect. They correspond with the expectation of general clinical observers in the grouping of sites of lesions giving a common initial epileptic disturbance. It is interesting to see how often the focus of discharge was far forward in the frontal lobe in those with initial unconsciousness. But it is the exceptions to the general rule that seem so important—the 2 cases out 10 with initial unconsciousness in whom the discharge arose more posteriorly; the adversive attacks with turning of eyes to or from the side of the discharge; and the scatter in subjects with epigastric sensations. Although the ability to relate a patient's experience to the expected site of a lesion is the basis of clinical neurology it is the individual deviation that excites the cerebral physiologist. This little paper has no more than passing interest for him, except in so far as the authors have integrated it into Dr. Penfield's other work, with its great accuracy of observation and rigidity of interpretation.

In dealing with the clinical application of their maps of cortical characteristics (reminiscent in this field, of Brodman's and the Vogt's in another) they reserve the word epilepsy, "for those cases in which no brain lesion or cortical focus can be demonstrated" and say that "major seizures in idiopathic epilepsy begin with the minor seizure or *petit mal* characteristic for that patient," in these patients "the Jacksonian march is unheard of." This may just be a difference in definition, but it does suggest that the nature of epilepsy, as we understand it, is being ignored through meticulous interest in the nature of the epileptic focus, for after all generalized convulsions are much more common than focal ones.

Study of the epileptic focus would teach us something about epilepsy just as study of cortical dysfunction in epilepsy would teach us something about cortical function, but in neither case should the particular observation be directly applied to the general subject.

D. W.

A Synopsis of Neurology. By W. F. Tissington Tatlow, J. A. Ardis and J. A. R. Bickford. Bristol: John Wright and Sons Ltd. Price 30s.

This new addition to Wright's well-known Synopsis series is composed of two distinct parts, Neuroanatomy which incidentally contains, as is both right and proper, accounts of function as well as of structure, and Clinical Neurology. Both parts should prove useful to students and practitioners. On the whole the section on Neuroanatomy is the better and the more valuable. Covering 205 out of a total number of 473 pages this part is a compressed but admirable description of the anatomy of the central nervous system and also includes the autonomic nervous system and the cerebrospinal fluid. The anatomical diagrams form a special feature, since the great majority are new and original and all are clear and informative. The busy practitioner and even the neurologist, whose anatomical memory may be a trifle rusty, should certainly find this part of the book a handy work of reference.

The section on clinical neurology suffers inevitably from the syncopated style necessary in a book of this kind. With a few exceptions it is readable and reliable. The ancillary diagnostic measures of radiology and angiography are described briefly but adequately for a book of the kind, and the book concludes with a short but useful account of clinical electroencephalography.

The chief criticism that may fairly be made is that there is too often a failure to make it clear to the reader what is common and what is rare in the clinical features of many conditions. And a number of statements are made with which all neurologists will certainly not agree and some which call for correction. For example in regard to the ætiology of disseminated sclerosis we are told that

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"pregnancy is a definite factor," and further that in this disease "multiple patches of gliosis occur anywhere in the *grey* matter of brain and cord." Under the heading of the tabetic arthropathies there is no mention of the hip-joint being affected and the reader is left to suppose that affections of the shoulder, elbow and wrist are only slightly less common than of the knee-joint, which is very far from being the case.

A. F.

The Normal Cerebral Angiogram. By ARTHUR ECKER, M.D., Ph.D. (Neurology), Surgical Neurologist, Syracuse, New York. Pp. 190, Illustrations 140. Blackwell Scientific Publications, Oxford. Price 47s.

This book is brief but comprehensive, and extremely well illustrated by diagrams, photographs and reproductions of X-ray films. The author describes his very practical methods of angiography by the percutaneous route, and gives full consideration to the details of injection and its possible difficulties and complications.

In the section on angiographic anatomy full use is made of variation in projection and the normal appearances, variants and some artefact appearances are described and well illustrated. Dr. Ecker uses compression to obtain some of his filling effects to a greater extent than is usual in this country and perhaps than some workers would consider desirable. He mentions no complications arising from this source in what is evidently a considerable experience. He has made some interesting observations on the relation of vessels to the free edge of the tentorium and their displacement by pressure.

This is a stimulating and well produced book, which will interest the experienced and the inexperienced alike.

H. D.

A Textbook of Clinical Neurology. By ISRAEL S. WECHSLER. 7th Edition. 1952. W. B. Saunders, Philadelphia and London. (Price not stated.)

The seventh addition of this well-known American textbook is stated to have been so thoroughly revised as to be in many ways quite new. Since its aim is to provide a textbook of clinical neurology it does not include any chapters on neuroanatomy or physiology. While many of the chapters are certainly satisfactory on the clinical side and especially in regard to symptomatology, the information provided on pathology is scanty. It is surprising to find in a textbook for undergraduates such very detailed information on the subject of intelligence tests, while other and more important practical instruction is lacking. Thus, for example, in the discussion of lead neuropathy there is no mention at all of the mechanism of production of lead neuritis nor any details at all of the treatment of this serious condition. The reader will seek in vain for details of real value on the subjects of ventriculography, angiography or electroencephalography.

The accounts of cervical rib and of the scalenus anticus syndrome are meagre and do less than justice to the importance of the subject.

And what benefit can a student receive from the concluding sentence of the remarks on the subject of the treatment of post-herpetic pain which runs . . . "and one wonders about cordotomy"?

Details of treatment are not always up to date, at any rate to British notions. Thus there is no mention of the value of intravenous injections of calcium salts in tetany or of the treatment of the spasms of tetanus by either avertin or the newer muscular relaxants such as curarine or myanesin.

To the reviewer it is very doubtful if such subjects as Raynaud's disease, thrombo-

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angiitis obliterans, scleroderma and angioneurotic œdema should be included in a textbook of neurology. In this book the accounts of these conditions are sketchy and inferior to what a student ought to expect in a textbook of general medicine; hence they occupy space which might have been devoted to pure neurological subjects. An unusual and attractive feature of the book is the concluding chapter on the history of neurology.

A. F.

Erkrankungen des Nervensystems. By F. ROEDER. Pp. 611. Figs. 137. Musterschmidt Wissenschaftlicher Verlag, Gottingen.

Though somewhat shorter this text greatly resembles in scope and plan the text of Schaltenbrand recently noticed in this Journal.

Its principal merit is the detail in which the clinical part of the book is dealt with, and it is free from the sketchy inadequacy which characterizes so many modern textbooks of clinical neurology in respect of their descriptions of disease. The clinical tradition, if we are to judge from these two recent German texts, is still strong in the country of their origin, and thus as a reference book of clinical neurology it is to be commended.

It suffers, however, from its failure to embody recent knowledge both in pathology and treatment, and much of the material under these headings might have been written fifteen years ago.

Thus neurosyphilis is still treated by mercurial inunction, and tabes by intrathecal salvarsan (Swift-Ellis), and the use of penicillin is discussed in a paragraph in small type.

The pathology of herpes zoster and poliomyelitis are similarly out of date.

Multiple peripheral neuritis has the old-fashioned list of "causes," but there is no reference to recent knowledge that biochemistry has thrown on the ætiology of this malady. Thoracic inlet syndromes and sciatica are also very inadequately discussed.

There was much virtue in the neurological textbooks of a generation ago. These virtues survive in this work, but something more is now needed to give it the usefulness it might so easily have.

F. M. R. W.

The Diagnosis of Nervous Diseases. By the late Sir JAMES PURVES-STEWART and C. WORSTER-DROUGHT. Tenth Edition. London: Edward Arnold and Co. Price 50s.

The tenth edition of this familiar book now appears for the first time under a joint authorship, the new author being Dr. Worster-Drought. He is to be congratulated on the results of his labours of re-editing and re-writing, which have undoubtedly brought the book up to date, although they have unfortunately added to its size and weight. It is perhaps permissible to suggest that in the next edition an attempt should be made to shorten the book by a more drastic pruning of some of the less common matters described in smaller print and to omit altogether old and now largely outmoded conceptions, such as that of the so-called varicose or phlebogenic form of sciatica. These few criticisms apart, it is a book which can be heartily recommended to the budding neurologist as well as to the senior student and practitioner. A valuable feature is the first section of no less than 103 pages on physiological anatomy. The adequate accounts of herniated cervical discs, compression of the median nerve in the carpal tunnel and of toxoplasmosis will serve as examples of the manner in which recent work has been incorporated. We have no doubt that this new edition will continue to receive the popularity accorded to its many predecessors.

A. F.

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